12 December 2024
EMA/18540/2025
Committee for Medicinal Products for Human Use (CHMP)

Type II variation assessment report

Procedure No. EMEA/H/C/005756/II/0004

Invented name: Apretude

International non-proprietary name: cabotegravir

Marketing authorisation holder (MAH): ViiV Healthcare B.V.

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

Status of this report and steps taken for the assessment			
Current step	**Description**	**Planned date**	**Actual Date**
☐	Start of procedure	22 Jul 2024	22 Jul 2024
☐	CHMP Rapporteur Assessment Report	20 Aug 2024	20 Aug 2024
☐	PRAC Rapporteur Assessment Report	23 Aug 2024	22 Aug 2024
☐	PRAC members comments	28 Aug 2024	28 Aug 2024
☐	Updated PRAC Rapporteur Assessment Report	29 Aug 2024	n/a
☐	PRAC endorsed relevant sections of the assessment report	05 Sep 2024	05 Sep 2024
☐	CHMP members comments	09 Sep 2024	09 Sep 2024
☐	Updated CHMP Rapporteur Assessment Report	12 Sep 2024	13 Sep 2024
☐	Request for Supplementary Information	19 Sep 2024	19 Sep 2024
☐	Submission of Responses	12 Nov 2024	11 Nov 2024
☐	Re-start of procedure	13 Nov 2024	13 Nov 2024
☐	CHMP Rapporteur Assessment Report	27 Nov 2024	28 Nov 2024
☐	PRAC Rapporteur Assessment Report	18 Nov 2024	18 Nov 2024
☐	PRAC members comments	20 Nov 2024	20 Nov 2024
☐	Updated PRAC Rapporteur Assessment Report	21 Nov 2024	n/a
☐	PRAC endorsed relevant sections of the assessment report	28 Nov 2024	28 Nov 2024
☐	CHMP members comments	02 Dec 2024	02 Dec 2024
☐	Updated CHMP Rapporteur Assessment Report	05 Dec 2024	n/a
☒	Opinion	12 Dec 2024	12 Dec 2024

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List of Abbreviations

AE	Adverse event
AESI	Adverse event(s) of special interest
AIDS	Acquired immunodeficiency syndrome
ALT	Alanine aminotransferase
ART	Antiretroviral therapy
ARV	Antiretroviral
AUC0-τ	Area under the concentration-time curve over the dosing interval
BMI	Body mass index
C0	Pre-dose (trough) concentration
CAB	Cabotegravir
cART	Combination antiretroviral therapy
Cavg	Average plasma concentration
CDC	Centers for Disease Control
CI	Confidence interval
CK	Creatine kinase
Cmax	Maximum plasma concentration
CSR	Clinical study report
Cτ	Trough concentration at the end of the dosing interval
CVb	Coefficient of variation between participants
CVF	Confirmed virological failure
DAIDS	Division of AIDS
EU	European Union
GCP	Good Clinical Practice
HCP	Health care practitioner
HIV	Human immunodeficiency virus
HPTN	HIV Prevention Trials Network
IM	Intramuscular
IMPAACT	International Maternal Pediatric Adolescent AIDS Clinical Trials
INSTI	Integrase strand transfer inhibitor
IQR	Interquartile range
ISR	Injection site reaction
LA	Long-acting injectable, extended-release suspension for injection, or prolonged release suspension for injection
LLOQ	Lower limit of quantification
LSFU	Long-term safety and washout pharmacokinetic follow-up
MedDRA	Medical Dictionary for Regulatory Activities
mg	milligram
MOCHA	More Options for Children and Adolescents
MSM	Men who have sex with men
NDA	New Drug Application
NQ	Not quantifiable
OLE	Open-label extension
OLI	Oral lead-in
PA-IC90	Protein adjusted 90% inhibitory concentration

PBMI	time-varying BMI
pcVPC	Prediction-corrected visual predictive check
PID	Participant indentifier
PK	Pharmacokinetic
PO	Oral administration
PopPK	Population pharmacokinetics
PrEP	Pre-exposure prophylaxis
PT	Preferred Term
Q1, Q3	Interquartile range
Q2M	Dosing every 2 weeks
Q4W	Dosing every 4 weeks (monthly)
Q8W	Dosing every 8 weeks (every 2 months)
RPV	Rilpivirine
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SMQ	Standardized MedDRA Query
SOC	System organ class
Study 208580	MOCHA; IMPAACT◦2017
TGW	Transgender women
TMF	Trial master file
tNDA	Treatment New Drug Application
TQT	Thorough QT Study
ULN	Upper limit of normal
US	United States

1. Background information on the procedure

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, ViiV Healthcare B.V. submitted to the European Medicines Agency on 24 May 2024 an application for a variation.

The following changes were proposed:

Variation requested		**Type**	**Annexes affected**
C.I.4	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	Type II	I, IIIA and IIIB

Update of sections 4.8, 5.1 and 5.2 of the SmPC to include data from clinical studies in HIV-1 uninfected adolescents (HPTN 083-01 and HPTN 084-01), updated data from the MOCHA study and updated PK data based on a population PK analysis of cabotegravir in adolescents in MOCHA, HPTN 083-01 and HPTN 084-01. In addition, the MAH took the opportunity to update section 4.2 of the SmPC to clarify the wording related to missed doses of oral PrEP and renal impairment, and to implement editorial changes in the SmPC. Furthermore, the MAH took the opportunity to align the PI with the latest QRD template version 10.4. The RMP version 1.1 has also been submitted.

The requested variation proposed amendments to the Summary of Product Characteristics, Labelling and Package Leaflet and to the Risk Management Plan (RMP).

2. Overall conclusion and impact on the benefit/risk balance

The current variation provides supplemental additional pharmacokinetic (PK) and safety information supporting the use of long-acting cabotegravir (CAB LA) for pre-exposure prophylaxis (PrEP) in adolescents weighing at least 35 kg who are at risk of sexually acquired HIV-1 infection.

PK and safety findings from the following CAB PrEP Studies: Study 213002 / HPTN 083-01 and Study 213003 / HPTN 084-01 were submitted along with data from the adolescent cabotegravir/ rilpivirine (RPV) treatment Study 208580 (IMPAACT 2017; MOCHA) which provided supportive safety information and informed the CAB PopPK model.

Studies HPTN 083-01 and HPTN 084-01 are single-arm, open-label studies focusing on safety, tolerability, and acceptability in sexually active, healthy adolescents assigned male or female at birth, respectively. These sub-studies were conducted alongside the parent protocols for the PrEP indication in adult males (HPTN 083) and females (HPTN 084). The PK analysis included 9 male and 53 female participants who entered the Injection Phase at Week 5 following the Oral Phase. Of these, 7 males and 52 females received all 5 CAB LA injections as per the approved Q2M (every two months) PrEP regimen.

Before the initiation injection, the overall geometric mean Week 5 concentration was 4.70 µg/mL for adolescent males and 2.11 µg/mL for females. The overall variability in CAB concentrations before the injection phase was high (CVb of 402% for males and 1088% for females), indicating poor adherence to oral lead-in dosing. This variability decreased to 38.6% and 29.1% at Week 41, following the final injection, for males and females, respectively. The trough concentrations observed in adolescents 8 weeks after the 5th injection (Week 41) were comparable to those in adults. For example, the geometric mean Week 41 CAB concentration in adolescent females under 50 kg was 3.52 µg/mL, slightly higher than the 3.09 µg/mL observed in those 50 kg or more. In adult women, the geometric mean Week 41 CAB concentration was 3.10 µg/mL for those under 50 kg and 2.54 µg/mL for those 50 kg or more.

Study 208580 is a Phase 1/2, multicenter, open-label, non-comparative study examining the safety, acceptability, tolerability, and PK of oral and LA injectable CAB and LA injectable RPV in virologically suppressed HIV-infected adolescents aged 12 to under 18 years and weighing at least 35 kg. The analysis included available PK sample data up to and including Cohort 2 Week 24. The observed PK profiles met the key exposure targets based on adult data, confirming appropriate doses for adolescents.

The previous CAB PopPK model was updated and refined with adolescent data from Studies 208580, 213002 and 213003. The adjustment of the initial model developed with the adult data to the additional paediatric data resulted in very similar model parameters with percentual differences that are generally lower than 10% except in some inter-individual variability (IIV) and covariance parameters. Regarding the quality of the model as judged by the goodness-of-fit (GOF) and visual predictive checks (VPCs), it can be considered acceptable. This final PopPK model was used to derive individual CAB exposure parameters for the respective participants. Post hoc CAB exposure was similar between adolescent participants from Studies 213002 and 213003 and adult participants from historical CAB studies.

The final refined CAB PopPK model was used to perform simulations supporting CAB dosing every 8 weeks (Q8W) for CAB PrEP in male and female adolescent participants under various scenarios. The observed CAB plasma concentrations over nominal times were similar across all studies and between male and female participants following the CAB Q8W regimen. Post hoc CAB PK exposure parameters (AUC0-τ, Cmax, and Cτ) in adolescents were similar to those in the adult population, including at Q8W steady state. Additionally, post hoc PK parameters were similar across the subgroups by sex assigned at birth and body weight following CAB Q8W regimen administration. The evaluated CAB dosing regimen in adolescents achieves exposures comparable to those in adults and is expected to result in similar efficacy observed in pivotal PrEP adult clinical studies. Data from Studies 213002 and 213003 in adolescents supported this expectation. As of the analysis dates (24 October 2022 for Study 213002 and 21 July 2022 for Study 213003), zero HIV infections were identified during the Oral Run-in Phase and Injection Phase. No relationship between plasma concentrations for CAB and safety parameters was observed in adults, and none is expected in adolescents. The review of safety data in adolescents from Studies 213002 and 213003 did not identify any new safety concerns or signals for CAB.

Studies HPTN 083-01 / HPTN 084-01 did not include efficacy endpoints and efficacy data from Study 208580 are not relevant to this variation. As of the analysis dates (24 October 2022 for Study 213002 and 21 July 2022 for Study 213003), no HIV infections were identified during the Oral Run-in Phase and Injection Phase.

Regarding safety, CAB PrEP in adolescents was well-tolerated. Overall, adverse event data from the HPTN 083-01 and HPTN 084-01 studies in adolescents did not show any new emergent safety concerns when compared with the known safety profile of CAB PrEP for adults (HPTN 083 and HPTN 084 studies). No new safety concerns emerged from the findings through week 16 of cohort 1C of supportive Study 208580, which enrolled 30 HIV-adolescents participants who received CAB in addition to combination antiretroviral therapy.

The RMP version 1.2 has been submitted. The main changes are as follows:

- supplemental data from the HPTN 083-01 and 084-01 adolescent studies
- updates to the clinical trial exposure
- inclusion of the approved protocol for the additional Pharmacovigilance - APR study

The changes to the RMP are acceptable.

The benefit-risk balance of Apretude remains unchanged.

3. Recommendations

Based on the review of the submitted data, this application regarding the following change:

Variation requested		Type	Annexes affected
C.I.4	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	Type II	I, IIIA and IIIB

Update of sections 4.8 and 5.2 of the SmPC to include data from clinical studies in HIV-1 uninfected adolescents (HPTN 083-01 and HPTN 084-01), updated data from the MOCHA study and updated PK data based on a population PK analysis of cabotegravir in adolescents in HPTN 083-01, HPTN 084-01 and MOCHA. In addition, the MAH took the opportunity to update section 4.2 of the SmPC to clarify the wording related to missed doses of oral PrEP and renal impairment and to implement editorial changes in the SmPC. Furthermore, the MAH took the opportunity to align the PI with the latest QRD template version 10.4 and update the list of local representatives. The RMP version 1.2 has also been adopted.

☒ is recommended for approval.

Amendments to the marketing authorisation

In view of the data submitted with the variation, amendments to Annex(es) I, IIIA and IIIB and to the Risk Management Plan are recommended.

4. EPAR changes

The table in Module 8b of the EPAR will be updated as follows:

Scope

Please refer to the Recommendations section above

Summary

Please refer to Scientific Discussion 'Apretude-H-C-005756-II-0004'

Annex: CHMP and PRAC assessment comments on the type II variation

5. Introduction

The current variation provides supplemental additional PK and safety data to support the ongoing use of CAB LA for PrEP in adolescents weighing at least 35 kg who are at risk of sexually acquired HIV-1 infection.

6. Clinical Pharmacology aspects

Apretude (CAB LA) was approved in at-risk adults and adolescents weighing at least 35 kg for PrEP to reduce the risk of sexually acquired HIV-1 infection. This approval was based on studies HPTN 083/213002 and HPTN 084/213003 in adult males and females, respectively. The current submission provides additional PK data on CAB LA use in adolescents at risk for HIV acquisition. It is provided supplemental information supporting the use of CAB LA for PrEP in adolescents weighing at least 35 kg who are at risk of sexually acquired HIV 1 infection. Data from the adolescent CAB/RPV treatment Study 208580 (IMPAACT 2017; MOCHA) informed the CAB PopPK model; therefore, information from Study 208580 is also included below.

6.1. Methods – analysis of data submitted

Study HPTN 083-01 is an ongoing single-arm, open-label, safety, tolerability, and acceptability study in sexually active, healthy adolescents assigned male sex at birth. There was no treatment randomisation due to this study being a single-arm, open-label study. This study in adolescent males is the sub-study to the parent protocol (HPTN 083) in adult males. Study participation included a Step 1 – Oral Run-in Phase, of up to 5 weeks of oral CAB 30 mg once daily safety lead-in and a Step 2 – Injection Phase, where a series of 5 IM injections of 3 mL (600 mg) were administered in the gluteal muscle at 8 week intervals after a 4-week loading dose (injections at Weeks 5, 9, 17, 25 and 33). After 5 injections in Step 2, participants could choose to continue CAB LA or receive oral TDF/FTC in the Step 3 Follow-up phase as described below. After conclusion of this 48-week period or if participants discontinued before 48 weeks, participants were transitioned to locally available care. Finally, Step 3 – Follow-up Phase starts with a blood draw visit, the +8 Week Visit, following the last injection to monitor CAB drug concentrations. Additional blood was collected at the +12, +24, +36, and +48 Week Visits. The PK analysis included 9 participants who entered the Injection Phase at Week 5 following the Oral Phase. Participants were scheduled to receive 5 CAB LA injections of the approved Q2M PrEP regimen; 7 of 9 participants received all 5 injections.

Study HPTN 084-01 is an ongoing single-arm, open-label, safety, tolerability, and acceptability study in sexually active, healthy adolescents assigned female sex at birth. There was no treatment randomization due to this study being a single-arm, open-label study. This study in adolescent females is the sub-study to the parent protocol (HPTN 084) in adult females. A similar to Study HPTN 083-01 Step 1, Step 2 and Step 3 study participation was also considered. The PK analysis includes 53 participants who entered the Injection Phase at Week 5 following the Oral Phase. 52 participants received all 5 CAB LA injections of the approved Q2M PrEP regimen.

Study 208580 is an ongoing Phase 1/2, multicenter, open label, non-comparative study of the safety, acceptability, tolerability, and PK of oral and LA injectable CAB and LA injectable RPV in virologically suppressed HIV-infected adolescents 12 to <18 years of age and weighing at least 35 kg who are receiving stable combination anti-retroviral therapy (cART) consisting of 2 or more drugs from 2 or more classes of ARV drugs. Adolescent, HIV-1 infected participants have been enrolled in Cohort 1 and assigned to Cohort 1C or Cohort 1R based on their background cART regimen. Following enrolment, participants received at least 4 weeks of OLI of CAB or RPV while continuing their background cART (Cohort 1 Step 1) for assessing

tolerability before starting the LA injections of the assigned drug. For participants enrolled under Protocol Version 2.0, LA injections were administered Q4W for a total of 3 injections while continuing the background cART (Cohort 1 Step 2). For participants enrolled under Protocol Version 3.0, LA injections were administered Q8W for a total of 2 injections while continuing the background cART (Cohort 1 Step 2). In addition to the participants enrolling directly into Cohort 2, adolescents who participated in Cohort 1 Step 2 could continue study participation in Cohort 2, if eligible. These participants could screen and enrol into Cohort 2 either prior to completing all scheduled LSFU study visits or resuming study participation after having already exited the study. Cohort 2 participants discontinued their pre-study cART regimen and received both CAB and RPV at the doses established in Cohort 1. Cohort 1 data indicated that the adult Q8W dosing regimen was appropriate for adolescents. Therefore, based on enrolment under Protocol Version 3.0, all Cohort 2 participants were scheduled to receive oral CAB + oral RPV for 4 to 6 weeks (Step 3) followed by CAB LA + RPV LA injections administered Q8W through Week 96 (Step 4).

Details of the CAB or RPV dosing for Cohort 1 are as follows:

- CAB (Cohort 1C) – CAB 30 mg once daily orally for at least 4 weeks (up to a maximum of 6 weeks) in addition to cART (Step 1), followed by 3 IM injections of CAB LA for Q4W regimen, each separated by 4 weeks (600 mg for the first injection and 400 mg for the second and third injections) or followed by 2 IM injections of CAB LA for Q8W regimen, each separated by 4 weeks, in addition to cART (Step 2).

- RPV (Cohort 1R) – RPV 25 mg once daily orally for at least 4 weeks (up to a maximum of 6 weeks) in addition to cART (Step 1), followed by 3 IM injections of RPV LA for Q4W regimen, each separated by 4 weeks (900 mg for the first injection and 600 mg for the second and third injections) or followed by 2 IM injections of RPV LA for Q8W regimen, each separated by 4 weeks (both 900 mg), in addition to cART (Step 2).

Details of the CAB or RPV dosing for Cohort 2 are as follows:

- Oral CAB 30 mg + oral RPV 25 mg once daily for 4 to 6 weeks (Step 3)
- CAB LA (600 mg) + RPV LA (900 mg) Q8W through Week 96 (Step 4)

The PK analysis includes all participants in the All-Treated Population who received at least 1 dose of treatment:

- Cohort 1: n=30 participants in Cohort 1C (including 8 Cohort 1C Q4W and 22 Cohort 1C Q8W participants)
- Cohort 2: n=144 participants in Cohort 2 (including 44 participants who had previously participated in Cohort 1).

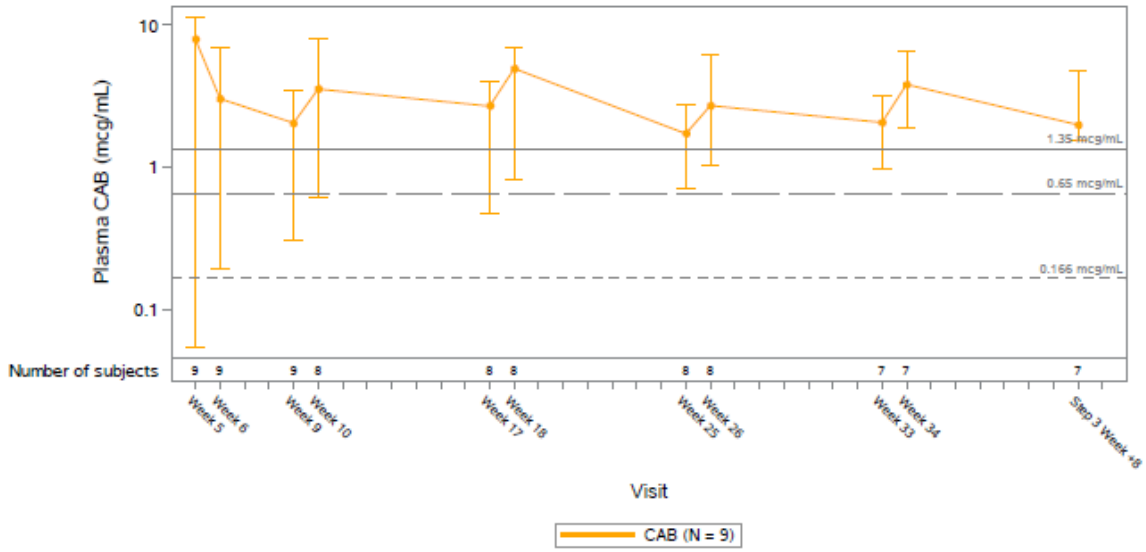
The analysis included available PK sample data up to and including Cohort 2 Week 24. In addition, plasma concentrations from some participants in LSFU were available and were included in plasma concentration listings.

6.2. Results

From Study HPTN 083-01, CAB concentration-time data are presented graphically for the overall population in Figure 1. Plasma CAB concentrations are summarized by visit for the overall population in table 1.

Plasma CAB trough concentrations (at the end of the dosing interval) are shown by concentration ranges in adolescent males

Figure 1. Median (min, max) CAB concentration-time data following administration of CAB LA Q8W in adolescent male participants in HPTN 083-01 (N=9)



Source: Study 213002 CSR Figure 7.013.
Note: Min, max=5th, 95th percentiles.
Note: Horizontal reference lines: Short dash 0.166 µg/mL= in vitro 1x PA-IC90. Long dash 0.65 µg/mL=predicted 5th percentile for Q8W administration (~4x PA-IC90). Solid line 1.35 µg/mL=observed geometric mean plasma concentration for 10 mg daily oral dosing (~8x PA-IC90), which is the target median trough concentration for CAB LA.
Note: Participants who had a concentration value below the LLOQ (0.025 µg/mL) had the concentration value imputed to half of the LLOQ.
Note: "Visit" has been adjusted to the planned injection visit when the participant received an injection late at a visit that was not an injection visit.

Table 1. Summary of plasma CAB concentrations at select visits following CAB LA in adolescent males in HPTN 083-01 (N=9)

	Overall[a] (N=9)	
Visit	**n/imputed**	**Plasma CAB (µg/mL)[b]**
Week 5 (predose Injection 1) (24h post last oral dose)	9/0	4.70 [1.29, 17.2] 402 (0.0549, 11.5)
Week 6 (1-week post Injection 1)	9/0	2.12 [0.883, 5.09] 163 (0.195, 6.94)
Week 9 (predose Injection 2) (After initiation injection)	9/0	1.52 [0.837, 2.76] 90.8 (0.310, 3.50)
Week 17 (predose Injection 3)	8/0	2.078 [1.16, 3.72] 78.7 (0.476, 3.99)
Week 25 (predose Injection 4)	8/0	1.70 [1.17, 2.46] 46.8 (0.713, 2.78)
Week 33 (predose Injection 5)	7/0	2.01 [1.43, 2.83] 38.0 (0.968, 3.21)
Week 34 (1 week post Injection 5)	7/0	3.81 [2.60, 5.57] 43.0 (1.91, 6.59)
Week 41 (8 weeks post Injection 5)	7/0	2.18 [1.54, 3.07] 38.6 (1.56, 4.72)

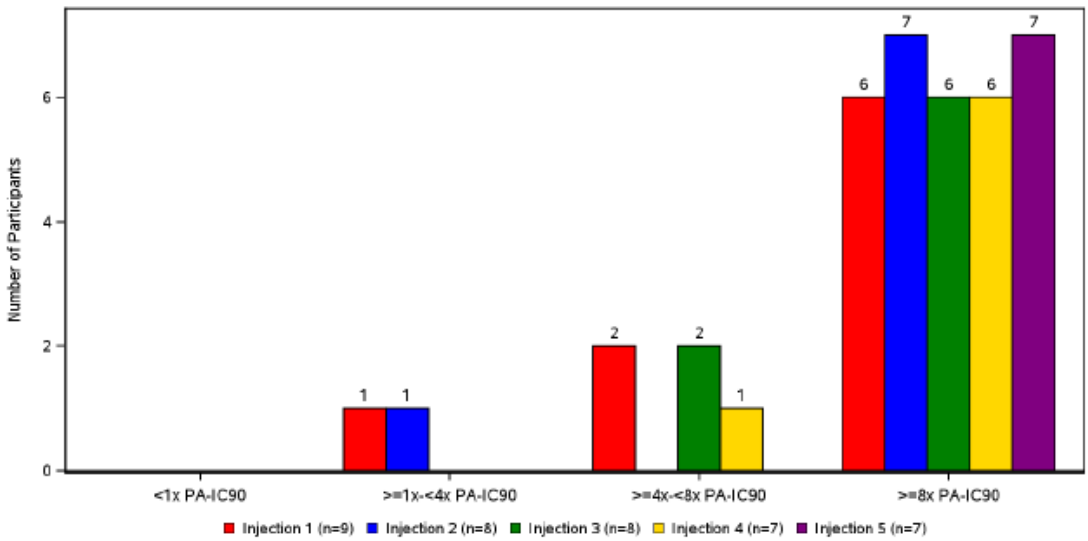
Visit	Overall[a] (N=9)	
	n/imputed	Plasma CAB (μg/mL)[b]

Source: Study 213002 CSR Table 7.004.

Note: 1 participant discontinued treatment and did not have PK data after Week 9. 1 participant missed injection 5 (Week 33) and re-continued CAB LA in Step 3 (Week +24) and thus did not have PK data at Week 33 to Week 41.

- Median age [IQR] (range) 17 [16, 17] (15 - 17) years; Median weight [IQR] (range) 70.6 [65.8, 83.7] (63 -167) kg.
- Geometric mean [95% CI]; CVb% (5th, 95th percentiles). Note 5th, 95th percentiles=min, max.

Figure 2. Number of participants in CAB Cτ ranges by injection visit (N=9)



Source: Study 213002 CSR Figure 7.014.

Note: PA-IC90=0.166 μg/mL, 4x PA-IC90=0.664 μg/mL, 8x PA-IC90=1.328 μg/mL.

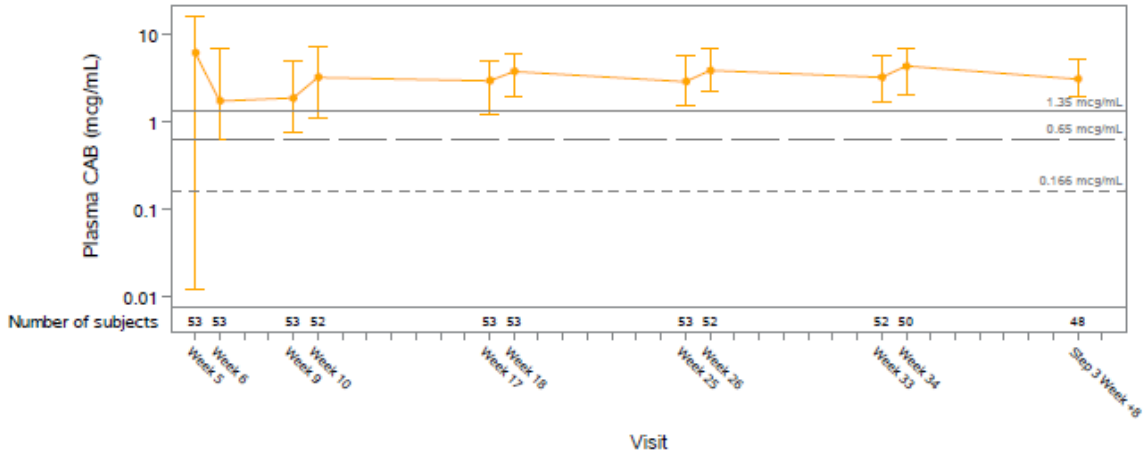
Note: Cτ=concentration at the end of the dosing interval prior to the next injection or 8 weeks following the final injection (injection 5).

Note: Injection 1=Week 9 Cτ; Injection 2=Week 17 Cτ; Injection 3=Week 25 Cτ; Injection 4=Week 33 Cτ; Injection 5=Week 41 Cτ.

Observed CAB LA PK in adolescent males was consistent with observed PK in adults in the parent study, HPTN 083. The overall geometric mean (min, max) trough concentration 8 weeks following the 5th injection (Week 33+8, Week 41) was 2.18 μg/mL (1.56, 4.72), which is 43% higher than the predose trough concentration at Week 9 (4 weeks following the 1st injection) of 1.52 μg/mL (0.310, 3.50). In comparison, the overall geometric mean (5th, 95th percentile) Week 41 CAB concentration in adult males (n=56) 8 weeks following the 5th injection was 1.63 μg/mL (0.50, 4.15). Overall variability in CAB concentrations prior to the initiation injection phase was high and consistent with potential poor adherence to oral lead-in dosing. Overall variability in CAB concentrations decreased from the initial to final injection, consistent with relatively high adherence to the injection schedule. There were no trough concentrations below PA-IC90 (Protein adjusted 90% inhibitory concentration) following any injection.

From **Study HPTN 084-01**, CAB concentration-time data are presented graphically for the overall population in Figure 3. Plasma CAB concentrations are summarized by visit by age group (<16 years, ≥16 years) and for the overall population in Table 2 and by weight range (<50 kg, ≥50 kg) in Table 3. Plasma CAB trough concentrations (at the end of the dosing interval) are shown by concentration ranges in Figure 3.

Figure 3. Median (5th, 95th percentile) CAB concentration-time data following administration of CAB LA Q8W in adolescent girls (N=53)



Source: Study 213003 CSR Figure 7.013.

Note: Horizontal reference lines: Short dash 0.166 µg/mL= in vitro 1x PA-IC90. Long dash 0.65 µg/mL=predicted 5th percentile for Q8W administration (~4x PA-IC90). Solid line 1.35 µg/mL=observed geometric mean plasma concentration for 10 mg daily oral dosing (~8x PA-IC90), which is the target median trough concentration for CAB LA.

Note: Participants who had a concentration value below the LLOQ had the concentration value imputed to half of the LLOQ. The LLOQ for CAB was 0.025 µg/mL.

Note: "Visit" has been adjusted to the planned injection visit when the participant received an injection late at a visit that was not an injection visit.

Table 2. Summary of plasma CAB concentrations at select visits following CAB LA in participants <16 years and ³16 years and overall (N=53)

Visit	Age <16 years[a] (N=15)		Age ≥16 years[b] (N=38)		Overall (n=53)	
	n/ imputed[c]	Plasma CAB (µg/mL)[d]	n/ imputed[c]	Plasma CAB (µg/mL)[d]	n/ imputed[c]	Plasma CAB (µg/mL)[d]
Week 5 (predose Injection 1) (24h post last oral dose)	15/4	0.325 [0.072, 1.48] (4202) (NQ, 17.2)	38/0	4.42 [2.80, 6.96] (240) (0.157, 16.7)	53/4	2.11 [1.15, 3.85] (1088) (NQ, 16.7)
Week 6 (1-week post Injection 1)	15/0	1.48 [0.982, 2.23] (85.8) (0.551, 5.96)	38/0	2.11 [1.69, 2.64] (76.8) (0.692, 7.44)	53/0	1.91 [1.57, 2.32] (81.0) (0.639, 6.92)
Week 9 (predose Injection 2) (After initiation injection)	15/0	1.98 [1.25, 3.16] (101) (0.676, 8.63)	38/0	1.97 [1.63, 2.38] (62.5) (0.812, 4.93)	53/0	1.97 [1.65, 2.36] (72.7) (0.779, 5.07)
Week 17 (predose Injection 3)	15/0	2.48 [1.94,3.18] (47.1) (1.22, 4.85)	38/0	2.91 [2.58, 3.28] (37.8) (1.65, 5.16)	53/0	2.78 [2.50, 3.10] (40.8) (1.23, 5.16)
Week 25 (predose Injection 4)	15/0	2.58 [2.08, 3.20] (40.3) (1.36, 5.05)	38/0	3.17 [2.84, 3.54] (34.2) (1.55, 5.94)	53/0	2.99 [2.71, 3.30] (37.0) (1.55, 5.72)

Visit	Age <16 years[a] (N=15)		Age ≥16 years[b] (N=38)		Overall (n=53)	
	n/ imputed[c]	Plasma CAB (μg/mL)[d]	n/ imputed[c]	Plasma CAB (μg/mL)[d]	n/ imputed[c]	Plasma CAB (μg/mL)[d]
Week 33 (predose Injection 5)	15/0	2.97 [2.49, 3.55] (32.6) (1.46, 4.99)	37/0	3.34 [2.97, 3.76] (36.2) (1.75, 5.90)	52/0	3.23 [2.94, 3.55] (35.3) (1.75, 5.74)
Week 34 (1-week post Injection 5)	15/0	3.38 [2.81, 4.05] (33.7) (1.89, 5.69)	35/0	4.41 [3.94, 4.94] (33.9) (2.59, 7.57)	50/0	4.07 [3.69, 4.50] (36.0) (1.74, 7.90)
Week 41 (8 weeks post Injection 5)	15/0	3.01 [2.60, 3.48] (26.8) (1.66, 4.35)	33/0	3.31 [2.98, 3.67] (30.0) (2.01, 5.29)	48/0	3.21 [2.96, 3.49] (29.1) (2.01, 5.27)

Source: Study 213003 CSR Table 7.004.

- Median (range) 15 (12 to 15) years; 56 (44.1 to 73.1) kg.
- Median (range) 17 (16 to 17) years; 54.75 (39.9 to 80.8) kg.
- NQ values were imputed to ½ LLOQ (0.0125 μg/mL) for statistical summaries.
- Geometric mean [95% CI] (CVb%) (5^{th}, 95^{th} percentiles) Note 5^{th}, 95^{th} percentiles=min, max for <16 years age group.

Table 3. Summary of plasma CAB concentrations at select visits following CAB LA in participants <50 kg and ³50 kg

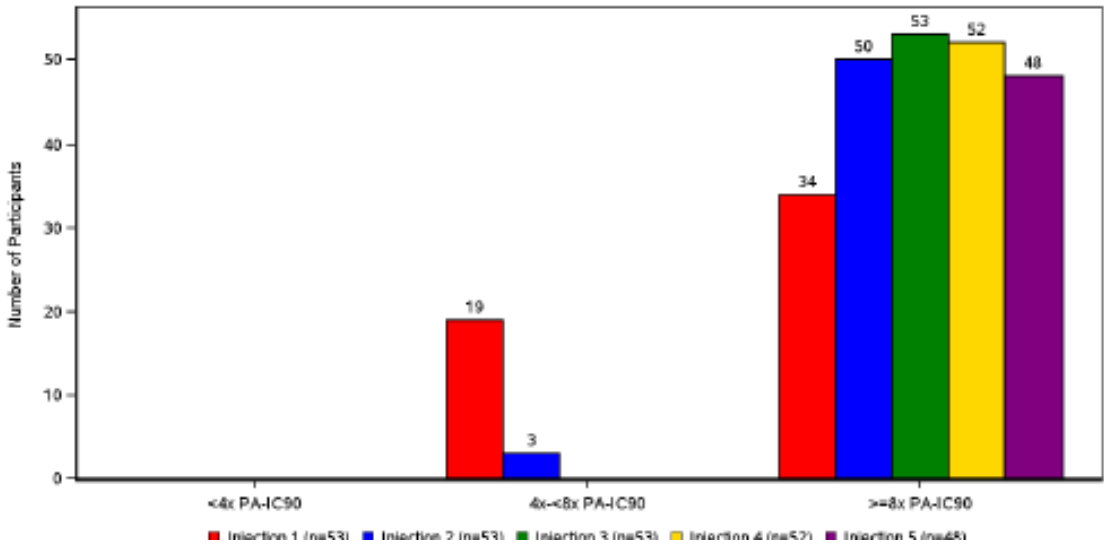
Visit	Weight <50 kg[a] (N=15)		Weight ≥50 kg[b] (N=38)	
	n/ imputed[c]	Plasma CAB (μg/mL)[d]	n/ imputed[c]	Plasma CAB (μg/mL)[d]
Week 5 (predose Injection 1) (24h post last oral dose)	15/1	1.72 [0.436, 6.75] (2130) (NQ, 18.6)	38/3	2.29 [1.15, 4.55] (888) (NQ, 15.6)
Week 6 (1-week post Injection 1)	15/0	3.64 [2.52, 5.26] (74.5) (1.14, 10.4)	38/0	1.48 [1.24, 1.78] (60.0) (0.590, 4.45)
Week 9 (predose Injection 2) (After initiation injection)	15/0	2.86 [2.10, 3.89] (60.1) (1.14, 7.17)	38/0	1.71 [1.39, 2.10] (70.3) (0.684, 5.07)
Week 17 (predose Injection 3)	15/0	3.10 [2.68, 3.59] (27.0) (1.88, 5.16)	38/0	2.67 [2.32, 3.07] (44.9) (1.22, 5.16)
Week 25 (predose Injection 4)	15/0	3.33 [2.83, 3.93] (30.3) (2.18, 6.03)	38/0	2.87 [2.54, 3.24] (38.8) (1.53, 5.05)
Week 33 (predose Injection 5)	14/0	3.59 [2.98, 4.34] (33.5) (1.83, 6.98)	38/0	3.11 [2.77, 3.48] (35.6) (1.62, 5.74)
Week 34 (1-week post Injection 5)	14/0	4.29 [3.52, 5.23]	36/0	3.99 [3.54, 4.50]

Visit	Weight <50 kg[a] (N=15)		Weight ≥50 kg[b] (N=38)	
	n/ imputed[c]	Plasma CAB (μg/mL)[d]	n/ imputed[c]	Plasma CAB (μg/mL)[d]
		(35.4) (2.03, 6.55)		(36.5) (1.89, 7.57)
Week 41 (8 weeks post Injection 5)	14/0	3.52 [3.02, 4.10] (27.1) (2.42, 5.50)	34/0	3.09 [2.80, 3.42] (29.4) (1.99, 5.25)

Source: Study 213003 CSR Table 7.006.

- Median (range) 46.7 (39.9 to 49.9) kg.
- Median (range) 58.7 (50 to 80.8) kg.
- NQ values were imputed to ½ LLOQ (0.0125 μg/mL) for statistical summaries.
- Geometric mean [95% CI] (CVb%) (5th, 95th percentiles) Note 5th, 95th percentiles=min, max for <50 kg weight group.

Figure 4. Number of participants in CAB Cτ ranges by injection visit (N=53)



Source: Study 213003 CSR Figure 7.014.
Note: PA-IC90=0.166 μg/mL, 4x PA-IC90=0.664 μg/mL, 8x PA-IC90=1.328 μg/mL.
Note: Cτ=concentration at the end of the dosing interval prior to the next injection or 8 weeks following the final injection (injection 5).
Note: Injection 1=Week 9 Cτ; Injection 2=Week 17 Cτ; Injection 3=Week 25 Cτ; Injection 4=Week 33 Cτ; Injection 5=Week 41 Cτ.

The overall geometric mean (5th, 95th percentile) trough concentration 8 weeks following the 5th injection (Week 33+8, Week 41) was 3.21 μg/mL (2.01, 5.27), which is 63% higher than the predose trough concentration 4 weeks following the 1st injection of 1.97 μg/mL (0.779, 5.07). In comparison, the overall geometric mean (5th, 95th percentile) Week 41 CAB concentration in adult women (n=150) 8 weeks following the 5th injection was 2.57 μg/mL (2.44, 2.71). Observed CAB LA PK in adolescent females was consistent with observed PK in adults in the parent study HPTN 084. Overall variability in CAB concentrations prior to the injection phase was high and consistent with reported poor adherence to oral lead-in dosing. Overall variability in CAB concentrations decreased from the initial to final injection, consistent with relatively high adherence to the injection schedule. There were no trough concentrations below 4x PA-IC90

following any injection. CAB PK was similar in participants <16 years and ≥16 years. When summarized by weight, CAB PK was slightly higher in participants <50 kg as compared to those ≥50 kg.

From **study 208580**, cohort 1C, Table 4 summarizes the observed CAB PK parameters after 2 weeks on the OLI regimen. These data represent the steady state PK of CAB administered orally as a 30 mg once daily regimen.

Table 1. Summary of CAB parameters following oral administration of CAB 30 mg once daily (Step 1) (Cohort 1C All Treated Population): Study 208580 full Cohort 1 analysis

PK parameter	Cohort 1C Q4W[a] (N=8)	Cohort 1C Q8W[a] (N=22)	Cohort 1C total[a] (N=30)
Number of participants with results	8	21	29
Cmax (μg/mL)	10.5 [8.28, 13.3] 10.1 (7.66, 17.3)	8.36 [6.84, 10.2] 8.94 (3.54, 21.0)	8.90 [7.61, 10.4] 9.28 (3.54, 21.0)
AUC0-τ[b] (h·μg/mL)	171 [126, 232] 160 (94.3, 325)	128 [98.1, 168] 122 (37.2, 433)	139 [113, 171] 148 (37.2, 433)
Tmax (h)	N/A 2.46 (1.05, 4.10)	N/A 3.00 (0.00, 4.10)	N/A 2.93 (0.00, 4.10)
Cτ[b] (μg/mL)	4.76 [2.99, 7.56] 5.25 (1.97, 10.6)	3.61 [2.43, 5.37] 3.75 (0.320, 21.0)	3.89 [2.87, 5.28] 4.04 (0.320, 21.0)

Source: Study 208580 W24 CSR Table 4.3.

- Data presented are geometric mean [95% CI]; median (min, max).
- τ is dosing interval (24 hours for oral CAB).

A sparse PK sampling scheme was employed during the injection phase (Cohort 1C Step 2; Week 4 through Week 16). CAB PK parameters after IM administration (injections at Weeks 4b, 8, and 12 for the Q4W regimen; injections at Weeks 4b and 8 for the Q8W regimen) including Injection 1 Cmax and Tmax for CAB and pre-dose concentrations are summarized in Table 5. The Cmax for CAB after the first injection was reflective of oral dosing, because the initial injection was administered together with the last oral dose of study drug in OLI.

Table 2. Summary of CAB PK parameters following IM administration (Cohort 1C All Treated Population): Study 208580 full Cohort 1 analysis

PK parameter[a]	Cohort 1C Q4W (N=8)	Cohort 1C Q8W (N=22)
Number of participants with results at each timepoint	8	21
Injection 1 Cmax[b] (μg/mL)	9.56 [7.36, 12.4] 9.73 (6.50, 17.9) 6.50, 17.9	6.42 [5.34, 7.72] 6.75 (2.48, 15.4) 2.60, 14.9
Injection 1 Tmax (h)	N/A 1.59 (0.200, 1.97) 0.200, 1.97	N/A 2.00 (-1.77[c], 2.15) -1.39, 2.15

PK parameter[a]	Cohort 1C Q4W (N=8)	Cohort 1C Q8W (N=22)
Number of participants with results at each timepoint	8	21
Week 4b C0[d] (μg/mL)	5.46 [3.97, 7.51] 5.63 (2.50, 9.44) 2.50, 9.44	2.89 [1.64, 5.11][d] 3.47 (0.0250, 11.9) 0.156, 11.7
Week 8 C0 (μg/mL)	2.10 [1.55, 2.83] 2.24 (1.01, 3.43) 1.01, 3.43	1.33 [0.903, 1.97] 1.64 (0.227, 6.02) 0.244, 5.82
Week 12 C0 (μg/mL)	2.73 [1.54, 4.81] 3.08 (0.616, 5.34) 0.616, 5.34	2.28 [1.60, 3.27] 2.93 (0.391, 9.88) 0.413, 9.56
Week 16 C0[e] (μg/mL)	2.91 [1.84, 4.59] 3.11 (1.22, 6.19) 1.22, 6.19	1.01 [0.538, 1.88][d] 1.15 (0.0250, 5.29) 0.0257, 5.17

Source: Study 208580 W24 CSR Table 4.1 and Table 4.4.

- All C0 concentrations were taken pre-dose, aside from the Week 12 Q8W C0 concentration which is mid-dose.
- Cmax after the first injection was more reflective of oral dosing, because the initial injection was administered together with the last oral dose of study drug in OLI.
- A negative Tmax value for 1 participant resulted from the PK sample being recorded as taken 1.77 hours before the reference time (first CAB injection), which impacted both the minimum and the 5th percentile values.
- 1 (4.8%) participant at Week 4b and 1 (4.8%) participant at Week 16 had a concentration below the LLOQ; the concentrations were imputed as the LLOQ.
- C0 at Week 16 is equivalent to Cτ.

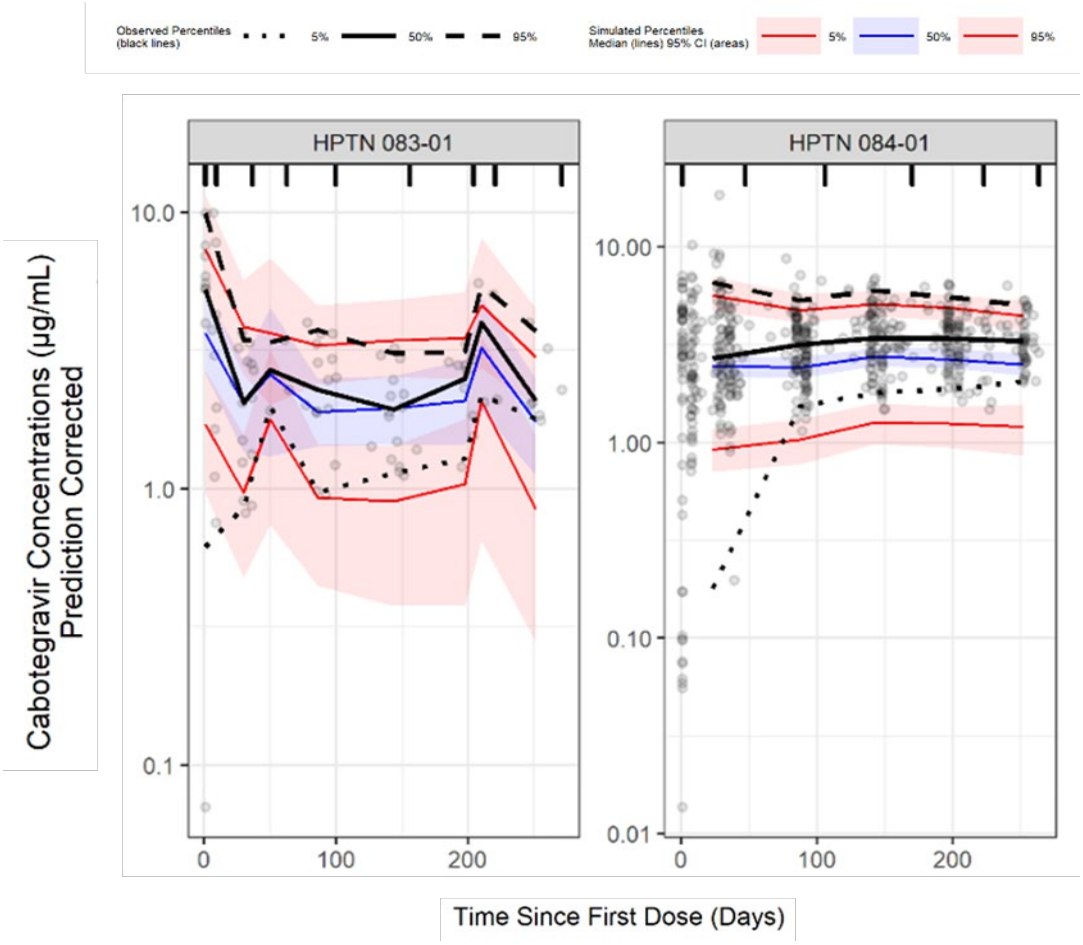
Regarding Cohort 2, the observed CAB PK parameters for Cohort 2 Week 24 following oral administration of 30 mg CAB once daily through Week 4a followed by IM Q8W administration show that C0 for CAB was generally consistent across Cohort 2 visits and between participants who had previously participated in Cohort 1 and participants who were new to the study.

Overall, rom this study, the observed PK profiles met the key exposure targets based on adult data for CAB (oral and IM administration), confirming that the doses are appropriate for adolescents.

The PK of CAB following PO and LA IM administration has been previously characterized using **popPK methods** in healthy participants and HIV1infected, treatment experienced adult participants (n=1647) by a linear 2-compartment model with first-order PO and LA IM absorption and first order elimination as the structural PK model. IIV was included on the KA1, KA2, CL/F, V2/F, and F1. The final covariate model in the same analysis revealed that weight was a significant determinant of CL/F, Q/F, V2/F, and V3/F, while smoking status was a significant determinant of CL/F only. Furthermore, needle length, female gender, splitting of the injection, and time-varying BMI were significant determinants of KA2. The existing adult CAB "tNDA" (treatment New Drug Application) PopPK model was used for further evaluate the PK of CAB in the adolescents. For that, external model validation was used to evaluate the adequacy of the previously developed adult CAB tNDA PopPK model to explain PK central tendency and variability in adolescents. The tNDA PopPK model parameters were re-estimated based on a new dataset including intensive and sparse concentration, dosing, demographic, and covariate data from adolescent participants in Studies 208580, 213002, and 213003. The external predictive performance of the tNDA PopPK model was evaluated using prediction- and simulation-based diagnostics. The final CAB PopPK model was then used to simulate plasma concentration-versus-time profiles of CAB in adolescent and adult participants, and subsequently used to derive individual secondary exposure parameters, in particular at steady state (AUC0-τ,ss, Cmax,ss, and Cτ,ss).

The previous PopPK model was updated and refined with adolescent data from Studies 208580, 213002, and 213003. In the final PopPK model, weight and smoking status were significant determinants of CL/F, and only weight was a determinant of V2/F, V3/F, and Q/F. Needle length, female gender, splitting of the injection, and time-varying BMI were significant determinants of KA2. No additional covariates were identified as compared to the tNDA PopPK model. The final PopPK model was able to predict the observed median and the 5th and 95th percentiles of observed CAB concentrations with reasonable accuracy. The median concentration was fully captured throughout the profile for CAB concentrations from Studies 213002/ HPTN 083-01 and 213003/ HPTN 084-01. pcVPCs stratified by study group are presented in Figure 5. The observed median was slightly outside the predicted bands for short segments of the time course but generally predicted well for adolescent participants from Studies 213002 and 213003.

Figure 5. pcVPC of the final CAB PopPK model



Source: Study Report TMF-16443596 Figure 12.

Notes: The open circles represent the observed data. The solid black lines represent the median of the observed data, and the dashed lines represent the 5th and 95th percentiles of the observed data. The blue solid lines represent the median of the simulated data, and the pink solid lines represent the 5th and 95th percentiles of the simulated data. The blue and pink shaded areas represent the 95% CI of the median and the 5th and 95th percentiles of the simulated data, respectively.

Post hoc CAB exposure was similar between the adolescent participants from Studies 213002 and 213003 and adult participants from historical CAB studies (Table 6).

Table 3. Summary of CAB post hoc exposure metrics by population (adult versus pooled adolescent participants from Studies 213002 (HPTN 083-01) and 213003 (HPTN 084-01)

Dosing phase		Adult participants			Adolescent participants from Studies 213002 (HPTN 083-01), and 213003 (HPTN 084-01)		
		AUC0-τ,ss (µg·h/mL)	Cmax,ss (µg/mL)	Cτ,ss (µg/mL)	AUC0-τ,ss (µg·h/mL)	Cmax,ss (µg/mL)	Cτ,ss (µg/mL)
OLI	N	1647	1647	1647	62	62	62
	Geomean [95% CI]	142 [140, 144]	7.59 [7.49, 7.69]	4.43 [4.37, 4.50]	221 [205, 238]	11.6 [10.8, 12.5]	7.15 [6.59, 7.76]
	%CV	87.1	83.7	93.5	90.8	87.5	96.1
	Median [min, max]	142 [49.5, 452]	7.59 [2.96, 22.6]	4.46 [1.16, 15.9]	221 [65.5, 413]	11.6 [3.60, 21.3]	7.19 [1.98, 13.9]
Dosing Phase		**Adult Participants**			**Adolescent Participants from Studies 213002 (HPTN 083-01) and 213003 (HPTN 084-01)**		
		AUC0-τ (µg·h/mL)	Cmax[a] (µg/mL)	Cτ (µg/mL)	AUC0-τ (µg·h/mL)	Cmax[a] (µg/mL)	Cτ (µg/mL)
Initial injection	Geomean [95% CI]	1577 [1545, 1609]	7.60 [7.50, 7.70]	1.45 [1.42, 1.48]	1965 [1754, 2201]	11.6 [10.8, 12.5]	1.73 [1.52, 1.97]
	%CV	116	83.5	120	122	87.5	134
	Median [min, max]	1609 [223, 5739]	7.59 [2.97, 22.6]	1.54 [0.164, 5.25]	1984 [358, 4453]	11.6 [3.60, 21.3]	1.81 [0.280, 4.07]
Dosing Phase		**Adult Participants**			**Adolescent Participants From Studies 213002 (HPTN 083-01) and 213003 (HPTN 084-01)**		
		AUC0-τ,ss (µg·h/mL)	Cmax,ss (µg/mL)	Cτ,ss (µg/mL)	AUC0-τ,ss (µg·h/mL)	Cmax,ss (µg/mL)	Cτ,ss (µg/mL)
SS Q8W maintenance regimen (6th LA IM injection)	Geomean [95% CI]	3625 [3580, 3672]	3.72 [3.66, 3.78]	1.67 [1.64, 1.70]	5348 [4959, 5766]	4.90 [4.49, 5.35]	2.96 [2.75, 3.18]
	%CV	82.9	94.4	105	91.3	101	88.9
	Median [min, max]	3673 [961, 11131]	3.77 [0.759, 11.1]	1.72 [0.203, 5.23]	5445 [1380, 9150]	5.04 [1.12, 8.75]	3.09 [0.923, 5.50]

Source: Study Report TMF-16443596 Table 18.

Note: Adolescent participants consist of participants from Studies 213002 (HPTN 083-01), and 213003 (HPTN 084-01). For AUC0-τ and Cτ, τ is different for different regimens. For time-varying BMI (designated as PBMI in the analysis dataset), BMI at time=0 was used for simulations. Post hoc simulations were performed without residual error.

Note: The standard Q4W and Q8W dosing regimens were simulated with oral lead-in: oral lead-in of CAB PO once daily for 4 weeks, followed by 600 mg CAB LA IM 2 hour after the last PO dose, followed by CAB LA IM 400 mg Q4W or 600 mg Q8W thereafter.

- The Cmax following the first CAB LA injection is likely determined by the last oral dose instead of the initiation LA dose.

The existing CAB PopPK model was developed with PK data from participants across several dosing regimens in adults and from adolescents. This model was employed to recommend appropriate dosing regimens and to predict exposures in the adolescent population. The observed CAB PK data from adolescent studies demonstrated that CAB exposures on oral and LA dosing are comparable in adolescents and adults. The data also demonstrated the adequate predictive capability of the PopPK model. Consequently, the PopPK model reliably supports the current CAB dosing regimens.

Post hoc PK exposure parameters (AUC0-τ, Cmax and Cτ) following administration of CAB Q8W regimen were slightly higher but comparable (overlapping 90% prediction intervals) to those in adults (Table 7). These increases can be attributed to the lower body weight of adolescents as compared with adults and are

not clinically relevant. Consistent with adults, there was no clinically significant impact of any covariates on CAB PK necessitating dose adjustment for individuals ≥ 35 kg (Table 7).

Median Cmax values in adolescents are below the 22.5 µg/mL geometric mean Cmax observed in the TQT study at the supratherapeutic dose of oral CAB at 150 mg (Table 7).

Table 4. Summary of post hoc CAB PK parameters in adolescents compared with adults following administration of proposed CAB dosing regimen

Population	Dosing Phase	Dosage Regimen	Plasma CAB PK Parameter Geometric Mean (5th, 95th percentile)		
			AUC0-τ (µg•h/mL)	Cmax (µg/mL)	Cτ (µg/mL)
Adolescents[a]	Oral Lead-In[c]	30 mg PO once daily	203 (136, 320)	10.7 (7.36, 16.6)	6.43 (4.15, 10.5)
	Initial Injection[d]	600 mg IM Initial Dose	2085 (1056, 4259)	10.8 (7.42, 16.6)	1.88 (0.801, 3.71)
	Every 2 months Injection[e]	600 mg IM Every 2 months	5184 (3511, 7677)	5.10 (3.06, 8.24)	2.54 (1.25, 4.19)
Adults[b]	Oral Lead-In[c]	30 mg PO once daily	145 (93.5, 224)	8.0 (5.3, 11.9)	4.6 (2.8, 7.5)
	Initial Injection[d]	600 mg IM Initial Dose	1591 (714, 3245)	8.0 (5.3, 11.9)	1.5 (0.65, 2.9)
	Every 2 months Injection[e]	600 mg IM Every 2 months	3764 (2431, 5857)	4.0 (2.3, 6.8)	1.6 (0.8, 3.0)

Source: Document No. TMF-16443596 Table 17 (adolescent data), Document No. 2018N384611 Table 17 (adult OLI and initial injection data), Document No. 2019N421460 Table 14 (Q8W injection data).

- PK parameter values were based on individual post hoc estimates from population PK models simulation in both a HIV-1 infected adolescent population (n = 147) weighing 35.2 -98.5 kg from Study 208580 and a HIV-1 uninfected adolescent population (n = 62) weighing 39.9 – 167 kg.
- For adults: PK parameter values were based on individual post-hoc estimates from population PK models for patients in Studies 201584 and 201585 for the oral, and initial regimen; and in Study 207966 for the every 2 month regimen.
- OLI PK parameter values represent steady state.
- Initial Injection Cmax values primarily reflect values following oral dosing because the initial injection was administered on the same day as the last oral dose.
- Every 2 months injection steady state: 6th CAB LA IM Injection (36-44 weeks after initiation injection).

6.3. Discussion

There are no new biopharmaceutic studies included in this submission. The bioanalytical methods used for Studies HPTN 083-01 / HPTN 084-01 and Study 208580 to measure concentrations of CAB in human plasma were the same as previously assessed. In these studies, the commercial formulations of CAB LA and CAB 30 mg tablets were used.

Studies HPTN 083-01 and HPTN 084-01 are single-arm, open-label studies focusing on safety, tolerability, and acceptability in sexually active, healthy adolescents assigned male or female at birth, respectively. These sub-studies were conducted alongside the parent protocols for the PrEP indication in adult males (HPTN 083) and females (HPTN 084). The PK analysis included 9 male and 53 female participants who

entered the Injection Phase at Week 5 following the Oral Phase. Of these, 7 males and 52 females received all 5 CAB LA injections as per the approved Q2M PrEP regimen.

Before the initiation injection, the overall geometric mean Week 5 concentration was 4.70 µg/mL for adolescent males and 2.11 µg/mL for females. The overall variability in CAB concentrations before the injection phase was high (CVb of 402% for males and 1088% for females), indicating poor adherence to oral lead-in dosing. This variability decreased to 38.6% and 29.1% at Week 41, following the final injection, for males and females, respectively. The trough concentrations observed in adolescents 8 weeks after the 5th injection (Week 41) were comparable to those in adults. For example, the geometric mean Week 41 CAB concentration in adolescent females under 50 kg was 3.52 µg/mL, slightly higher than the 3.09 µg/mL observed in those 50 kg or more. In adult women, the geometric mean Week 41 CAB concentration was 3.10 µg/mL for those under 50 kg and 2.54 µg/mL for those 50 kg or more.

Study 208580 is a Phase 1/2, multicenter, open-label, non-comparative study examining the safety, acceptability, tolerability, and PK of oral and LA injectable CAB and LA injectable RPV in virologically suppressed HIV-infected adolescents aged 12 to under 18 years and weighing at least 35 kg. The analysis included available PK sample data up to and including Cohort 2 Week 24. The observed PK profiles met the key exposure targets based on adult data, confirming appropriate doses for adolescents.

The previous CAB PopPK model was updated and refined with adolescent data from Studies 208580, 213002, and 213003. The adjustment of the initial model developed with the adult data to the additional paediatric data resulted in very similar model parameters with percentual differences that are generally lower than 10% except in some IIV and covariance parameters. Regarding the quality of the model, as judged by the GOF and VPCs, it can be considered acceptable. This final PopPK model was used to derive individual CAB exposure parameters for the respective participants. Post hoc CAB exposure was similar between adolescent participants from Studies 213002 and 213003 and adult participants from historical CAB studies.

The final refined CAB PopPK model was used to perform simulations supporting CAB Q8W dosing for CAB PrEP in male and female adolescent participants under various scenarios. The observed CAB plasma concentrations over nominal times were similar across all studies and between male and female participants following the CAB Q8W regimen. Post hoc CAB PK exposure parameters ($AUC_{0-\tau}$, C_{max}, and C_{τ}) in adolescents were similar to those in the adult population, including at Q8W steady state. Additionally, post hoc PK parameters were similar across the subgroups by sex assigned at birth and body weight following CAB Q8W regimen administration. The evaluated CAB dosing regimen in adolescents achieves exposures comparable to those in adults and is expected to result in similar efficacy observed in pivotal PrEP adult clinical studies. Data from Studies 213002 and 213003 in adolescents supported this expectation. As of the analysis dates (24 October 2022 for Study 213002 and 21 July 2022 for Study 213003), zero HIV infections were identified during the Oral Run-in Phase and Injection Phase. No relationship between plasma concentrations for CAB and safety parameters was observed in adults, and none is expected in adolescents. The review of safety data in adolescents from Studies 213002 and 213003 did not identify any new safety concerns or signals for CAB.

7. Clinical Efficacy aspects

The current variation provides supplemental additional PK and safety data to support the ongoing use of CAB LA for PrEP in adolescents weighing at least 35 kg who are at risk of sexually acquired HIV-1 infection.

Studies HPTN 083-01 / HPTN 084-01 did not include efficacy endpoints and efficacy data from Study 208580 are not relevant to this variation.

Virology data was obtained from these studies and it is discussed below.

7.1. Methods – analysis of data submitted

7.1.1. HPTN 083-01/ HPTN 084-01

These ongoing single-arm studies in sexually active, healthy adolescents included an analysis of HIV drug resistance among participants with confirmed HIV infection as a secondary objective.

7.1.2. Study 208580

Study 208550 is an ongoing Phase 1/2, multicenter, open-label, non-comparative study of the safety, acceptability, tolerability, and PK of oral and LA injectable CAB and LA injectable RPV in virologically suppressed HIV-infected adolescents at least 12 years of age and weighing at least 35 kg who were receiving stable cART consisting of 2 or more drugs from 2 or more classes of antiretroviral drugs. One of its objectives was to describe HIV-1 genotypic and phenotypic resistance patterns in participants experiencing virologic failure (Cohort 1 and Cohort 2).

7.2. Results

7.2.1. HPTN 083-01/ HPTN 084-01

- Of the 9 adolescents enrolled in HPTN 083-01, 0 HIV incident infections were identified at the time of the analysis (24 October 2022).
- Of the 55 adolescents enrolled in HPTN 084-01, 0 HIV incident infections were identified at the time of the analysis (21 July 2022).

7.2.2. Study 208580

A single incident of confirmed virologic failure (CVF) occurred during this study. Virologic failure was defined as 2 consecutive plasma HIV-1 RNA test results ≥ 200 copies/mL.

The CVF occurred in Cohort 1C Long-term safety and washout pharmacokinetic follow-up (LSFU); no resistance was observed at the CVF timepoint.

Participant [PPD redacted] (Cohort 1C) met CVF 46 weeks past their last CAB injection (LSFU Week 48) with an HIV-1 RNA of 8750 c/mL. This suspected virologic failure event was confirmed 4 weeks later with an HIV-1 RNA of 339 c/mL. Entry genotypic and phenotypic testing failed to yield results; therefore, it was not possible to assess potential preexisting resistance to CAB or RPV. Samples collected at the CVF visit showed no evidence of resistance to CAB or RPV.

9 months after the Cohort 1 LSFU Week 48 visit, the participant successfully screened for Cohort 2 and remains on study as of the data cutoff for the report. After an elevated HIV-1 RNA at Cohort 2 entry

(643 copies/mL), the participant is suppressed (HIV-1 RNA < 200 c/mL) on study treatment through Week 64.

7.3. Discussion

The following is a summary of virology results provided by the abovementioned studies:

- Of the 9 adolescents enrolled in HPTN 083-01, 0 HIV incident infections were identified at the time of the analysis (24 October 2022).
- Of the 55 adolescents enrolled in HPTN 084-01, 0 HIV incident infections were identified at the time of the analysis (21 July 2022),
- A single incident of CVF occurred during the MOCHA study (208580). The CVF occurred in Cohort 1C LSFU; no resistance was observed at the CVF timepoint.

This data provides additional support to the authorized therapeutic indication.

8. Clinical Safety aspects

TOPIC 1 – CLINICAL STUDIES

Safety findings from the CAB PrEP studies: Study 213002 / HPTN 083-01 and Study 213003 / HPTN 084-01 are presented to provide supplemental information supporting the use of CAB LA for PrEP in adolescents weighing at least 35 kg who are at risk of sexually acquired HIV-1 infection. Moreover, data from Study 208580 (MOCHA; IMPAACT 2017)—a study evaluating CAB treatment for adolescents living with HIV—which provide supportive safety information on the use of CAB in adolescents; are also presented. The HPTN 083-01/084-01 studies have been conducted by the HIV Prevention Trials Network (HPTN) and sponsored by the Division of AIDS (DAIDS), a Division of the National Institute of Allergy and Infectious Diseases (NIAID) which is an institute of the United States National Institute of Health (NIH). The MOCHA study is being conducted by IMPAACT and also sponsored by DAIDS

8.1. Methods

8.1.1. HPTN 083-01

HPTN 083-01 is an ongoing single-arm, open-label, safety, tolerability, and acceptability study in sexually active, healthy adolescents assigned male sex at birth. There was no treatment randomization due to this study being a single-arm, open-label study. This study in adolescent males is the sub-study to the parent protocol (HPTN 083) in adult males.

Study participation included:

Step 1 – Oral Run-in Phase

- Up to 5 weeks of oral CAB 30 mg once daily safety lead-in

Step 2 – Injection Phase

- A series of 5 IM injections of 3 mL (600 mg) CAB LA, administered in the gluteal muscle at 8-week intervals after a 4-week loading dose (injections at Weeks 5, 9, 17, 25, and 33).
- A safety visit followed each injection to ascertain safety data, including injection site reactions.
- Participants who discontinued study product during Step 2 for any reason other than HIV infection or AE occurrence related to study product were transitioned to open-label generic TDF/FTC or brand name TDF/FTC (Truvada) for 48 weeks.
- After 5 injections in Step 2, participants could choose to continue CAB LA or receive oral TDF/FTC in the Step 3 Follow-up phase as described below. After conclusion of this 48-week period or if participants discontinued before 48 weeks, participants were transitioned to locally available care.

Step 3 – Follow-up Phase

- Step 3 started with a blood draw visit, the +8 Week Visit, following the last injection to monitor CAB drug concentrations. Additional blood was collected at the +12, +24, +36, and +48 Week Visits.
- All participants who had received at least 1 injection were followed for 48 weeks after their last injection and had the choice of continuing on CAB LA or being provided with TDF/FTC.
- Participants were allowed to switch from TDF/FTC to CAB LA in Step 3, but it would not lengthen their Step 3.
- Waning concentrations of CAB (the PK tail) were covered with continued CAB LA or locally sourced oral generic TDF/FTC or brand name TDF/FTC (Truvada) for once daily use for 48 weeks.
- Behavioral and acceptability data were collected via CASI.

Note: Participants who elected to switch to oral PrEP were dispensed TDF/FTC at Week 34 (one week after the 5th injection at Week 33). They were instructed not to begin taking it until 8 weeks after the final injection (i.e., start of Step 3).

Finally, in-depth qualitative interviews were conducted near the end of Step 2 (at or around Week 34) to explore issues of acceptability and preference for oral tablets and/or injections.

8.1.2. HPTN 084-01

HPTN 084-01 is an ongoing single-arm, open-label, safety, tolerability, and acceptability study in sexually active, healthy adolescents assigned female sex at birth. There was no treatment randomization due to this study being a single-arm, open-label study. This study in adolescent females is the sub-study to the parent protocol (HPTN 084) in adult females.

Study participation included:

Step 1 – Oral Run-in Phase

- Up to 5 weeks of oral CAB 30 mg once daily safety lead-in

Step 2 – Injection Phase

- A series of 5 IM injections of 3 mL (600 mg) CAB LA administered in the gluteal muscle at 8-week intervals after a 4-week loading dose (injections at Weeks 5, 9, 17, 25, and 33).
- A safety visit followed each injection to ascertain PK-peak safety data, including injection site reactions.

- Participants who discontinued study product during Step 2 for any reason other than HIV infection or AE occurrence related to study product were transitioned to open-label generic TDF/FTC or brand name TDF/FTC (Truvada) for 48 weeks.
- After 5 injections in Step 2, participants could choose to receive oral TDF/FTC in the Step 3 Follow-up phase. Alternatively, once the HPTN 084 OLE study was available at their site, participants could join the HPTN 084 OLE to continue to receive CAB LA after completing their Week +8 Visit in Step 3 of HPTN 084-01.

Step 3 – Follow-up Phase

- Step 3 started with a blood draw visit, the +8 Week Visit, following the last injection to monitor CAB drug concentrations. Additional blood was collected at the +12, +24, +36, and +48 Week Visits.
- All participants who had received at least 1 injection were followed for 48 weeks after their last injection.
- Waning concentrations of CAB (the PK tail) were covered with locally sourced oral generic TDF/FTC or brand name TDF/FTC (Truvada) for once daily use for 48 weeks.
- Behavioral and acceptability data were collected via CASI.

Note: Participants were dispensed TDF/FTC at Week 34 (one week after the 5th injection at Week 33). They were instructed not to begin taking it until 8 weeks after the final injection (i.e., start of Step 3).

HPTN 084 OLE

- Participants were offered the option to enroll in the HPTN 084 OLE study if they wanted to remain on CAB LA.
- Participants who completed Step 2 (i.e., received all 5 CAB LA injections) and the Week +8 Visit of Step 3 could move to the HPTN 084 OLE study or those already in Step 3 could switch back to CAB LA in the HPTN 084 OLE study.

Finally, in-depth qualitative interviews were conducted at the end of the product exposure period (at or around Week 34) to explore issues of acceptability and preference for oral tablets and/or injections.

8.1.3. Supportive studies

Study 208580 (MOCHA; IMPAACT 2017) is an ongoing Phase 1/2, multicenter, open-label, non-comparative study of the safety, acceptability, tolerability, and PK of oral and LA injectable CAB and LA injectable RPV in virologically suppressed HIV-infected adolescents at least 12 years of age and weighing at least 35 kg who were receiving stable cART consisting of 2 or more drugs from 2 or more classes of ART drugs.

The study design included 2 cohorts of participants and 2 steps of study participation in each cohort. In Cohort 1, participants, in addition to continuing their pre-study cART regimen, received either oral CAB or oral RPV tablets (Step 1) followed by either CAB LA or RPV LA (Step 2). Cohort 1 participants were assigned either CAB (Cohort 1C) or RPV (Cohort 1R) based on their pre-study cART regimen. The cohorts and steps are described as follows:

Cohort 1

- Cohort 1C – Oral CAB 30 mg once daily for at least 4 weeks (up to a maximum of 6 weeks) in addition to cART (Step 1 Oral Phase), followed by 3 IM injections of CAB LA Q4W (600 mg for the first injection and 400 mg for the second and third injections) in addition to cART (Step 2).

- Cohort 1R – Oral 25 mg RPV once daily for at least 4 weeks (up to a maximum of 6 weeks) in addition to cART (Step 1 Oral Phase), followed by 3 IM injections of RPV LA Q4W (900 mg for the first injection and 600 mg for the second and third injections) in addition to cART (Step 2).
- Participants in Cohort 1 were to be followed for up to 64 weeks.

Cohort 2

- Oral 30 mg CAB + oral 25 mg RPV once daily for at least 4 weeks (up to a maximum of 6 weeks) (Step 3 Oral Phase), followed by IM injections of CAB LA + RPV LA: first and second injections 4 weeks apart (CAB LA 600 mg + RPV LA 900 mg), with subsequent injections every 8 weeks through and including Week 96 (Step 4 Injection Phase).
- Participants in Cohort 2 were to be followed for up to 96 weeks.

Table 8. Description of clinical safety studies

Protocol no.	No. study centers and locations	Study start; Enrollment status and date; Total/ target enrollment	Study objective	Study design	Diagnosis; key inclusion criteria	Treatment details (drug; dose; form; route; frequency; duration)	No. of participants by group entered/ completed; Sex (at birth) M/ F; Mean age (range)	Primary endpoint(s)
HPTN 083-01 (213002)	4 US	July 2020; Enrollment completed January 2022; 9/ 50	Primary: To evaluate the safety, tolerability and acceptability of CAB LA in healthy, HIV-uninfected male adolescents aged below 18 years.	Phase 2b multicenter, open-label, non-comparative study	Sexually active, HIV-uninfected healthy adolescents (below age 18 years of age and body weight ≥35 kg at enrollment) who were assigned male sex at birth	CAB 30 mg once daily orally for up to 5 weeks, followed by CAB LA 600 mg IM injection (gluteal muscle) at Weeks 5, 9, 17, 25, and 33	9/ 2; 9 M; 16.4 (15-17) years	Safety: Proportion of participants experiencing any Grade 2 or higher clinical AEs and laboratory abnormalities among participants who receive at least 1 injection of CAB LA; Tolerability: Proportion of participants who receive at least 1 injection and who discontinue receiving injections prior to the full course of injections due to intolerability of injection, frequency of injections or burden of study procedures; Acceptability: Proportion of participants who complete all scheduled injections and proportion of participants who receive at least one injection whom would consider using CAB LA for HIV prevention in the future

Protocol no.	No. study centers and locations	Study start; Enrollment status and date; Total/ target enrollment	Study objective	Study design	Diagnosis; key inclusion criteria	Treatment details (drug; dose; form; route; frequency; duration)	No. of participants by group entered/ completed; Sex (at birth) M/ F; Mean age (range)	Primary endpoint(s)
HPTN 084-01 (213003)	1 South Africa; 1 Uganda; 1 Zimbabwe	December 2020; Enrollment completed August 2021; 55/ 55	Primary: To evaluate the safety, tolerability and acceptability of CAB LA in healthy, HIV uninfected female adolescents aged below 18 years.	Phase 2b multicenter, open-label, non-comparative study	Sexua7lly active, HIV-uninfected healthy adolescents (below age 18 years of age and body weight ≥35 kg at enrollment) who were assigned female sex at birth	CAB 30 mg once daily orally for up to 5 weeks, followed by CAB LA 600 mg IM injection (gluteal muscle) at Weeks 5, 9, 17, 25, and 33	55/ 37; 55 F[b]; 16.0 (12-17) years	Safety: Proportion of participants who experienced any Grade 2 or higher clinical AEs and laboratory abnormalities from AE reporting among participants who received at least 1 injection of CAB LA. Tolerability: Proportion of participants who received at least 1 injection and who discontinued receiving injections prior to the full course of injections due to intolerability of injection, frequency of injections, or burden of study procedures. Acceptability: Proportion of participants who completed all scheduled injections and proportion of participants who received at least 1 injection who would consider using CAB LA for HIV prevention in the future.

Protocol no.	No. study centers and locations	Study start; Enrollment status and date; Total/ target enrollment	Study objective	Study design	Diagnosis; key inclusion criteria	Treatment details (drug; dose; form; route; frequency; duration)	No. of participants by group entered/ completed; Sex (at birth) M/ F; Mean age (range)	Primary endpoint(s)
208580 (MOCHA; IMPAACT 2017)	**Cohort 1** 15 sites: 8 US; 3 South Africa; 2 Botswana; 2 Thailand	**Cohort 1:** April 2019; Completed March 2022; 55 (30 in Cohort 1C; 25 in Cohort 1R)/ 55	Primary: To confirm doses and evaluate the safety, tolerability, acceptability, and PK of oral CAB, CAB LA, and RPV LA in virologically suppressed HIV-1-infected cART-experienced children and adolescents aged 12 to <18 years	Phase 1/ Phase 2 multicenter, open-label, non-comparative study	HIV-1-infected children and adolescents 12 to <18 years of age who are virologically suppressed	Cohort 1C[c]: cART + CAB 30 mg once daily orally for 4-6 weeks; then cART + CAB LA IM injections (initially IM injections of 600 mg for first injection and 400 mg for second and third injections, administered at Weeks 4, 8, and 12; after a protocol amendment, participants received IM injections of 600 mg at Weeks 4 and 8)	Cohort 1C[c]: Q4W: 8/ 8; Q8W: 22/ 21 Total: 30/ 29 (completed Week 16/Injection Phase); Cohort 1C[c] 16 M/ 14 F; 14.9 (12-17) years	N/A

a. There were no female (at birth) participants as only participants who were assigned male sex at birth were eligible to participate.
b. There were no male (at birth) participants as only participants who were assigned female sex at birth were eligible to participate.
c. Only findings from Cohort 1C of Study 208580 are applicable to this document and are included.

Assessor's comments

Safety findings from the CAB PrEP studies: Study 213002 / HPTN 083-01 and Study 213003 / HPTN 084-01 are presented to provide supplemental information supporting the use of CAB LA for PrEP in adolescents weighing at least 35 kg who are at risk of sexually acquired HIV-1 infection. The applicant presented separately the safety data from each of the pivotal studies, HPTN 083-01 and HPTN 084-01, as it concerns adolescent females and males at birth, respectively, as the sub-studies to the parent

protocols (HPTN 083 and HPTN 084). There was no treatment randomization due to these studies being a single-arm, open-label.

Updated data based on the Study 208580 (MOCHA; IMPAACT 2017)—a study evaluating CAB treatment for adolescents living with HIV— was also presented in this application and provided supportive safety information on the use of CAB in adolescents.

8.2. Results

8.2.1. Participant disposition, demographic characteristics, overall extent of exposure, & adherence (HPTN 083-01 and HPTN-04)

8.2.1.1. HPTN 083-01

Participant disposition

A total of 12 participants were screened, 9 participants were enrolled, and all 9 enrolled participants received study drug.

Table 9. HPTN 083-01: Summary of disposition and withdrawals (Enrolled Population)

	CAB (N=9) n (%)
Treatment (Steps 1 and 2)	
Completed[a]	8 (89)
Ongoing	0
Treatment discontinuation	1 (11)
Participant refused further study product use	1 (11)
Study status (including Follow-up [Step 3])	
Completed[b]	2 (22)
Ongoing	6 (67)
Study termination	1 (11)
Participant refused further study product use	1 (11)

Source: Study 213002 CSR Table 1.001
Participants who were followed for at least 28 weeks after their first injection in Step 2 or confirmed seroconverted were considered as having completed the treatment. 1 participant had only 4 injections during Step 2 (missed 5th scheduled injection) but was considered to have completed Step 2, entered Step 3, and continued to receive injections.
Participants who had scheduled exit visit/end of study or confirmed seroconverted were considered as completed the study.

Demographic characteristics

All HPTN 083-01 participants were adolescents ranging in age from 15 to 17 years old. Approximately half of the participants were White (56%), and the majority self-identified as male (67%) and bisexual (67%).

Table 10. HPTN 083-01: Participant demographics (Enrolled Population)

	CAB (N=9)
Age (years)	
Mean (SD)	16.4 (0.73)
Median	17.0
Minimum, maximum	15, 17
Age group	
≤16 years	4 (44)

	CAB (N=9)
>16 years	5 (56)
Race	
Black or African Americana	3 (33)
White	5 (56)
Mixed race	1 (11)
Sex assigned at birth	
Male	9 (100)
Self-identified gender	
Female	1 (11)
Gender variant or gender non-conforming	1 (11)
Male	6 (67)
Self-identify, other	1 (11)
Sexual orientation	
Gay/lesbian/homosexual	2 (22)
Bisexual	6 (67)
Additional category (pansexual)	1 (11)
Weight (kg)	
Mean (SD)	83.9 (32.83)
Median	70.6
Minimum, maximum	63, 167
BMI (kg/m2)	
Mean (SD)	26.38 (10.226)
Median	21.60
Minimum, maximum	20.0, 51.6

Source: Study 213002 CSR Table 1.006

- Black or African American is an FDA race category.

Overall extent of exposure

In HPTN 083-01, all 9 participants (100%) received oral study drug for the expected 5 weeks in Step 1. The median (minimum, maximum) exposure to study drug during the Oral Phase (Step 1) was 35.0 (31, 38) days. 7 of 9 participants (78%) who started Step 2 received all 5 injections, and 8 of 9 participants received study drug around the Week 33 visit as planned. The median (minimum, maximum) exposure to study drug overall throughout the study was 232.0 (36, 239) days.

Adherence

In HPTN 083-01 at Week 4, 2 participants (22%) had >100% adherence to oral study product, 5 participants (56%) had 90 to 100% adherence, and 1 participant (11%) had 80 to 89% adherence based on pill counts. 1 participant (11%) had missing data.

Most (70%) injection visits occurred "on time" (i.e., within a ±3 day window) relative to the projected dosing visit. 5 injection visits (11%) were missed during Step 2 of the study: 1 participant missed 4 injections due to discontinuing treatment; and 1 participant missed 1 injection in Step 2 but continued injections in Step 3.

8.2.1.2. HPTN 084-01

Participant disposition

A total of 69 participants were screened, 55 participants were enrolled, and all 55 enrolled participants received study drug.

Table 11. HPTN 084-01: Summary of disposition and withdrawals (Enrolled Population)

	CAB (N=55) n (%)
Treatment	
Completed[a]	52 (95)
Ongoing	0
Treatment discontinuation	3 (5)
Adverse event	2 (4)
Positive pregnancy test result	1 (2)
Study status	
Completed[b]	1 (2)
Completed based on entering HPTN 084 OLE[c]	36 (65)
Ongoing	15 (27)
Study termination	3 (5)
Adverse event	1 (2)
Participant refused further participation	2 (4)

Source: Study 213003 CSR Table 1.001

- Participants who received all 5 scheduled injections in Step 2 or confirmed seroconverted were considered as having completed the treatment.
- Participants who had scheduled exit visit/end of study or confirmed seroconverted were considered as completed the study.
- Participants who entered HPTN 084 OLE were considered as completing the HPTN 084-01 study at that time.

Demographic characteristics

All HPTN 084-01 participants were Black heterosexual female adolescents (ranging in age from 12 to 17 years old). The majority of participants weighed at least 50 kg.

Table 12. HPTN 084-01: Participant demographics (Enrolled Population)

	CAB (N=55)
Age (years)	
Mean (SD)	16.0 (1.12)
Median	16.0
Minimum, maximum	12, 17
Age group	
<16 years	15 (27)
≥16 years	40 (73)
Race	
Black or African American[a]	55 (100)
Sex assigned at birth	
Female	55 (100)
Self-identified gender	
Female	55 (100)
Sexual orientation	
Straight/heterosexual	55 (100)
Weight (kg)	
Mean (SD)	56.4 (8.89)
Median	55.7
Minimum, maximum	40, 81
BMI (kg/m2)	
Mean (SD)	22.55 (3.270)
Median	22.20
Minimum, maximum	15.8, 34.1

Source: Study 213003 CSR Table 1.006

- Black or African American is an FDA race category. There were no African American participants in this study. All participants in this study were Black Africans.

Overall extent of exposure

In HPTN 084-01, 53 of 55 participants (96%) received oral study drug for the expected 5 weeks in Step 1. The median (minimum, maximum) exposure to study drug during the Oral Phase (Step 1) was 35.0 (21, 45) days. 52 of 53 participants (98%) who started Step 2 received all 5 injections, all of whom received study drug around the Week 33 visit as planned. The median (minimum, maximum) exposure to study drug overall throughout the study was 231.0 (21, 240) days.

Adherence

In HPTN 084-01, the majority (69%) of participants had 90 to 100% adherence to oral study product at Week 4 based on pill counts. Most (87%) injection visits occurred "on time" (i.e., within a ±3 day window) relative to the projected dosing visit. No injection visits were missed prior to discontinuing study treatment.

Assessor's comments

In HPTN 083-01, all 9 participants (100%) received oral study drug in Step 1, 7 (78%) who started Step 2 received all 5 injections, and 8 participants received study drug around the Week 33 visit as planned. In HPTN 084-01, 53 of 55 participants (96%) received oral study drug in Step 1, 52 (98%) who started Step 2 received all 5 injections, all of whom received study drug around the Week 33 visit as planned. The median (min, max) exposure to study drug overall throughout the study was similar across the two studies: 232.0 (36, 239) days in HPTN 083-01 and 231.0 (21, 240) days in HPTN 084-01. Overall, adherence to study drug was high overall among participants in both studies. Although the duration of treatment and especially the sample size are limited, the patient exposure is considered acceptable for the purpose of this application. Of note, is also the supportive Study 208580 (MOCHA) that provides exposure data for the HIV-adolescent population (discussed below).

8.2.2. Adverse Events (HPTN 083-01 and HPTN-04)

8.2.2.1. Overview of adverse events

Safety data from the HPTN 083-01 and HPTN 084-01 PrEP studies in adolescents do not show or indicate any new safety concerns or signals compared with the safety profile of CAB PrEP for adults, as per the findings from the HPTN 083 and HPTN 084 PrEP studies in adults and currently approved product labelling.

HPTN 083-01

In HPTN 083-01, all 9 participants reported at least 1 AE during Step 1 and/or Step 2, approximately half (56%) of whom had AEs that were considered by the investigator to be drug related. In Step 2, approximately half of participants had ISRs, all of whom had AEs that were considered by the investigator to be drug related. All 9 participants reported at least 1 AE in Steps 1 and 2 that were Grade 2 to 5 (100%), of whom one-third (33%) had AEs that were considered by the investigator to be drug related; 22% of participants reported AEs in Steps 1 and 2 that were Grade 3 to 5. No participants reported an SAE or AE leading to discontinuation of study drug during Steps 1 and 2, and 1 participant had an SAE during Step 3 that was not considered by the investigator to be drug related. There were no fatal SAEs.

Table 13. HPTN 083-01: Overall summary of adverse events (adverse events in Steps 1 and 2 [Safety Population] and injection site reactions in Step 2 [Injection Population])

	CAB (N=9) n (%)
Any AE	9 (100)
Drug-related AEs	5 (56)
Any AE, excluding ISRs	9 (100)
Drug-related AEs, excluding ISRs	2 (22)
ISR AE[a]	5 (56)
Drug-related ISR AE[a]	5 (56)
Any Grade 2 to 5 AEs	9 (100)
Drug-related Grade 2 to 5 AEs	3 (33)
Grade 2 to 5 AEs, excluding ISRs	8 (89)
Drug-related Grade 2 to 5 AEs, excluding ISRs	0
Grade 2 to 5 ISR AEs[a]	3 (33)
Drug-related ISR Grade 2 to 5 AEs[a]	3 (33)
Any Grade 3 to 5 AEs	2 (22)
Drug-related Grade 3 to 5 AEs	0
Grade 3 to 5 AEs, excluding ISRs	2 (22)
Drug-related Grade 3 to 5 AEs, excluding ISR	0
Grade 3 to 5 ISR AEs[a]	0
Drug-related ISR Grade 3 to 5 AEs[a]	0
AEs leading to discontinuation of study drug	0
Drug-related AEs leading to discontinuation of study drug	0
ISRs leading to discontinuation of study drug	0
Any SAE	0
Drug-related SAEs	0
Fatal SAEs	0
Drug-related fatal SAEs	0

Source: Study 213002 CSR Table 1.003, Table 3.004, Table 3.005, Table 3.015 (Injection Population), Table 3.016, Table 3.017, Table 3.035, Table 3.047, Table 3.866

Note: Treatment causality (drug-related) was based on the Investigator's causality assessment.

- N in this category is the number of participants who received at least 1 injection of study drug (Injection Population) in Step 2 only (N=9).

HPTN 084-01

In HPTN 084-01, all participants reported at least 1 AE during Step 1 and/or Step 2, the majority of which were considered by the investigator to be drug related. In Step 2, approximately one quarter of participants had ISRs, all of which were considered by the investigator to be drug related.

Most participants reported at least 1 AE in Steps 1 and 2 that were Grade 2 to 5 (96%), and approximately half (47%) of participants experienced AEs that were considered by the investigator to be drug related; 18% of participants reported AEs in Steps 1 and 2 that were Grade 3 to 5. The proportion of participants with SAEs and AEs leading to discontinuation of study drug was low. No participants discontinued study drug due to ISRs. 2 participants (4%) reported SAEs during Steps 1 and 2 (each participant reported 1 SAE, neither of which were considered by the investigator to be drug related). An additional SAE occurred during the HPTN 084 OLE, which was not considered drug related by the investigator. There were no fatal SAEs.

Table 14. HPTN 084-01: Overall summary of adverse events (adverse events in Steps 1 and 2 [Safety Population] and injection site reactions in Step 2 [Injection Population])

	CAB (N=55) n (%)
Any AE	55 (100)
Drug-related AEs	37 (67)
Any AE, excluding ISRs	55 (100)
Drug-related AEs, excluding ISRs	34 (62)
ISR AE[a]	14 (26)
Drug-related ISR AE[a]	14 (26)
Any Grade 2 to 5 AEs	53 (96)
Drug-related Grade 2 to 5 AEs	26 (47)
Grade 2 to 5 AEs, excluding ISRs	53 (96)
Drug-related Grade 2 to 5 AEs, excluding ISRs	25 (45)
Grade 2 to 5 ISR AEs[a]	3 (6)
Drug-related ISR Grade 2 to 5 AEs[a]	3 (6)
Any Grade 3 to 5 AEs	10 (18)
Drug-related Grade 3 to 5 AEs	0
Grade 3 to 5 AEs, excluding ISRs	10 (18)
Drug-related Grade 3 to 5 AEs, excluding ISR	0
Grade 3 to 5 ISR AEs[a]	0
Drug-related ISR Grade 3 to 5 AEs[a]	0
AEs leading to discontinuation of study drug	2 (4)
Drug-related AEs leading to discontinuation of study drug	0
ISRs leading to discontinuation of study drug	0
Any SAE	2 (4)
Drug-related SAEs	0
Fatal SAEs	0
Drug-related fatal SAEs	0

Source: Study 213003 CSR Table 1.003, Table 3.003 (Injection Population), Table 3.004, Table 3.005, Table 3.009, Table 3.015 (Injection Population), Table 3.016, Table 3.017, Table 3.035, Listing 16.150, Table 3.047

Note: Treatment causality (drug-related) was based on the Investigator's causality assessment.

- N in this category is the number of participants who received at least 1 injection of study drug (Injection Population) in Step 2 only (N=53).

8.2.2.2. Common adverse events

HPTN 083-01

In HPTN 083-01, AEs in Steps 1 and 2 were reported most frequently from either the Investigations SOC (9 [100%] participants) or General disorders and administration site conditions SOC (5 [56%] participants).

The most commonly reported AEs are summarized in the table below. Creatinine renal clearance decreased was the most frequently reported AE PT in Steps 1 and 2.

During the Injection Phase (Step 2), 56% of participants reported ISRs, including injection site pain (56%) and injection site swelling (11%); the majority of participants had ISRs with a maximum intensity of Grade 1 (22%) or Grade 2 (33%).

Table 15. HPTN 083-01: Summary of common AEs (reported in at least 2 participants) – Steps 1 and 2 (Safety Population)

Preferred term	**CAB (N=9) n (%)**
Number of participants with any AE	9 (100)
Creatinine renal clearance decreased	6 (67)
Blood phosphorus decreased	5 (56)
Injection site pain	5 (56)
Proteinuria	4 (44)
Alanine aminotransferase increased	3 (33)

Preferred term	CAB (N=9) n (%)
Hyperglycaemia	3 (33)
Amylase increased	2 (22)
Aspartate aminotransferase increased	2 (22)
Blood calcium increased	2 (22)
Blood creatinine increased	2 (22)
Headache	2 (22)

Source: Study 213002 CSR Table 3.007

HPTN 084-01

In HPTN 084-01, AEs in Steps 1 and 2 were reported most frequently from either the Investigations SOC (55 [100%] participants) or Infections and infestations SOC (29 [53%] participants). The most commonly reported AEs are summarized in Table 16. Creatinine renal clearance decreased was the most frequently reported AE PT in Steps 1 and 2.

During the Injection Phase (Step 2), 26% of participants reported ISRs, including injection site pain (25%), injection site induration (4%), and injection site swelling (2%); the majority of participants had ISRs with a maximum intensity of Grade 1 (21%).

Table 16. HPTN 084-01: Summary of common AEs (reported in at least 5% of participants) – Steps 1 and 2 (Safety Population)

Preferred term	CAB (N=55) n (%)
Number of participants with any AE	55 (100)
Creatinine renal clearance decreased	41 (75)
Amylase increased	27 (49)
Blood glucose increased	22 (40)
Blood glucose decreased	21 (38)
Lipase increased	21 (38)
Amenorrhoea	14 (25)
Injection site pain	13 (24)
Blood alkaline phosphatase increased	12 (22)
Abnormal uterine bleeding	10 (18)
Blood bilirubin increased	9 (16)
Blood creatinine increased	9 (16)
Headache	9 (16)
Blood creatine phosphokinase increased	8 (15)
Blood phosphorus decreased	8 (15)
Proteinuria	8 (15)
Urinary tract infection	8 (15)
Alanine aminotransferase increased	7 (13)
Upper respiratory tract infection	6 (11)
Haemoglobin decreased	5 (9)
Abnormal loss of weight	4 (7)
Aspartate aminotransferase increased	4 (7)
Dizziness	4 (7)
Neutrophil count decreased	4 (7)
Blood calcium increased	3 (5)
Chlamydial infection	3 (5)
Constipation	3 (5)
Dermatitis allergic	3 (5)
Genitourinary chlamydia infection	3 (5)
Genitourinary tract gonococcal infection	3 (5)
Intermenstrual bleeding	3 (5)
Nausea	3 (5)
White blood cell count decreased	3 (5)

Source: Study 213003 CSR Table 3.007

8.2.2.3. Adverse events by intensity

HPTN 083-01

The majority of participants reported one or more AEs that were Grade 2 (78%). Grade 3 events were reported by 22% of participants. No participant reported a Grade 4 event. No Grade 5 (death) events occurred during the study.

The primary safety analysis included the number and percent of participants with any Grade 2 or higher AEs or laboratory abnormalities (reported as AEs) from the first injection visit to 8 weeks after the last Step 2 injection visit or Week 41, whichever came first. The most frequently reported Grade 2 or higher AE was creatinine renal clearance decreased (Table below).

Table 17. HPTN 083-01: Primary analysis of proportion and 95% confidence interval of all Grade 2 or higher adverse events – Step 2 (Injection Population)

	CAB (N=9)	
Preferred term	**n (%)**	**95% CI for percent**
Number of participants with any AE Grade 2 or higher	9 (100)	(66, 100)
Creatinine renal clearance decreased	6 (67)	(30, 93)
Injection site pain	3 (33)	(7, 70)
Alanine aminotransferase increased	1 (11)	(<1, 48)
Blood creatine phosphokinase increased	1 (11)	(<1, 48)
Blood creatinine increased	1 (11)	(<1, 48)
Headache	1 (11)	(<1, 48)
Hypertension	1 (11)	(<1, 48)
Injection site swelling	1 (11)	(<1, 48)
Limb injury	1 (11)	(<1, 48)
Lipase increased	1 (11)	(<1, 48)
Malaise	1 (11)	(<1, 48)
Rash	1 (11)	(<1, 48)
Vomiting	1 (11)	(<1, 48)

Source: Study 213002 CSR Table 3.027
Note: PTs are listed in the order of decreasing frequency.
Note: The 95% CI was calculated using the exact (Clopper-Pearson) method.

HPTN 084-01

The majority of participants reported one or more AEs that were Grade 2 (78%). Grade 3 events were reported by 16% of participants. One participant reported a Grade 4 event. No Grade 5 (death) events occurred on the trial.

The primary safety analysis included the number and percent of participants with any Grade 2 or higher AEs or laboratory abnormalities (reported as AEs) from the first injection visit to 8 weeks after the last Step 2 injection visit or Week 41, whichever came first. The most frequently reported Grade 2 or higher AE was creatinine renal clearance decreased (Table below).

Table 18. HPTN 084-01: Primary analysis of proportion and 95% confidence interval of Grade 2 or higher adverse events (reported in at least 2 participants) – Step 2 (Injection Population)

	CAB (N=53)	
Preferred term	**n (%)**	**95% CI for percent**
Number of participants with any AE Grade 2 or higher	50 (94)	(84, 99)
Creatinine renal clearance decreased	40 (75)	(62, 86)
Amylase increased	8 (15)	(7, 28)
Blood creatinine increased	8 (15)	(7, 28)
Abnormal uterine bleeding	7 (13)	(5, 25)
Blood glucose decreased	7 (13)	(5, 25)
Urinary tract infection	7 (13)	(5, 25)
Lipase increased	6 (11)	(4, 23)
Abnormal loss of weight	4 (8)	(2, 18)
Proteinuria	4 (8)	(2, 18)
Chlamydial infection	3 (6)	(1, 16)
Constipation	3 (6)	(1, 16)
Genitourinary chlamydia infection	3 (6)	(1, 16)
Genitourinary tract gonococcal infection	3 (6)	(1, 16)
Injection site pain	3 (6)	(1, 16)
Upper respiratory tract infection	3 (6)	(1, 16)
Bacterial vaginosis	2 (4)	(<1, 13)
Blood alkaline phosphatase increased	2 (4)	(<1, 13)
Blood bilirubin increased	2 (4)	(<1, 13)
Blood creatine phosphokinase increased	2 (4)	(<1, 13)
Dermatitis allergic	2 (4)	(<1, 13)
Intermenstrual bleeding	2 (4)	(<1, 13)
Neutrophil count decreased	2 (4)	(<1, 13)
Platelet count decreased	2 (4)	(<1, 13)
Skin laceration	2 (4)	(<1, 13)

Source: Study 213003 CSR Table 3.027
Note: PTs are listed in the order of decreasing frequency.
Note: The 95% CI was calculated using the exact (Clopper-Pearson) method.

8.2.2.4. Drug-related adverse events

HPTN 083-01

All participants in Steps 1 and 2 reported at least 1 AE. The proportion of participants who had events considered drug-related by the investigator was 5 (56%). The most frequently reported drug-related AE was injection site pain.

Two (22%) participants had non-ISR AEs that were considered drug related by the investigator. One participant developed a Grade 1 AE of amylase increased and the other participant developed Grade 1 AEs of fatigue and sleep disorder. Grade 2 or higher AEs reported as drug-related during Steps 1 and 2 occurred in 3 (33%) of participants. The drug-related events that were Grade 2 or higher were injection site pain (33%) and injection site swelling (11%). There were no Grade 3 or higher drug-related AEs reported during Steps 1 and 2.

Table 19. HPTN 083-01: Summary of drug-related adverse events in Steps 1 and 2 (Safety Population)

Preferred term	CAB (N=9) n (%)
Number of participants with any AE	5 (56)
Injection site pain	5 (56)
Amylase increased	1 (11)
Fatigue	1 (11)
Injection site swelling	1 (11)
Sleep disorder	1 (11)

Preferred term	CAB (N=9) n (%)

Source: Study 213002 CSR Table 3.048
Note: PTs are listed in the order of decreasing frequency.

HPTN 084-01

All participants in Steps 1 and 2 reported at least 1 AE. The proportion of participants who had events considered drug-related by the investigator was 37 (67%) (Table below) The most frequently reported drug-related AE was injection site pain.

The proportion of participants who had non-ISR AEs that were considered drug-related by the investigator was 34 (62%). The most frequently reported drug-related non-ISR AE was creatinine renal clearance decreased (12 participants [22%]).

Grade 2 or higher AEs reported as drug-related during Steps 1 and 2 occurred in 26 (47%) of participants. The most frequently reported drug-related events that were Grade 2 or higher were creatinine renal clearance decreased (12 participants [22%]) and amylase increased (6 participants [11%]). There were no Grade 3 or higher drug-related AEs reported during Steps 1 and 2.

Table 20. HPTN 084-01: Summary of common drug-related adverse events (reported in at least 5% of participants) in Steps 1 and 2 (Safety Population)

Preferred term	CAB (N=55) n (%)
Number of participants with any AE	37 (67)
Injection site pain	13 (24)
Creatinine renal clearance decreased	12 (22)
Lipase increased	11 (20)
Amylase increased	8 (15)
Blood bilirubin increased	7 (13)
Headache	5 (9)
Alanine aminotransferase increased	4 (7)
Blood alkaline phosphatase increased	4 (7)
Blood phosphorus decreased	4 (7)
Dizziness	4 (7)
Blood creatinine increased	3 (5)
Blood glucose decreased	3 (5)
Nausea	3 (5)
Proteinuria	3 (5)

Source: Study 213003 CSR Table 3.048
Note: PTs are listed in the order of decreasing frequency.

8.2.2.5. Deaths

No deaths occurred during HPTN 083-01 or HPTN 084-01.

8.2.2.6. Other serious adverse events

HPTN 083-01

No participants had an SAE during Steps 1 or 2 of this study. One participant had an SAE of suicidal ideation during Step 3 of this study but remained on CAB in Step 3 (Table below).

Table 21. HPTN 083-01: Listing of serious adverse events (Safety Population)

Participant ID (30008301-PID)	Step	Preferred term	Action with regard to study drug	Grade	Related[a]
[PPD redacted]	3	Suicidal ideation	Drug interrupted	4	No

Source: Study 213002 CSR Listing 16.140.
- Relationship to study drug as assessed by the investigator.
- The case narrative for the participant with an SAE is provided in Study 213002 CSR Section 13.1 and is verbatim below.

- **Participant** [PPD redacted] (Study 213002 CSR Section 13.1): experienced a Grade 4 event of Suicidal ideation 363 days since the start of CAB and 54 days since the last dose of CAB LA. This participant was transported to the emergency department by the police. A psychiatric assessment revealed that "harmful behaviours were present" and that he had a "high expressed emotion level within family and parent-child relational problems". The participant was transferred to an inpatient behavioural facility, continued Lexapro and was discharged with outpatient psychiatric follow-up. Although there was no prior report of depression or suicidal ideation, the participant suffered with anxiety and had been prescribed Lexapro (escitalopram) by a paediatrician and had been using this for 2 months. The last dose being administered on the same day the event occurred. He also had a pre-existing diagnosis of ADHD (attention deficit hyperactivity disorder) for which he was initially placed on dexmethylphenidate in 2018 and subsequently switched to lisdexamphetamine (Vyvance) in 2022 which was ongoing. Of note, the participant had a significant family history of psychiatric conditions. The investigator considered that there was no reasonable possibility that the suicidal ideation may have been caused by CAB but reported that other possible cause(s) of the event to be "concurrent medication" and that the hospitalization was not related to the study medication. The participant continued with CAB and made a recovery.

HPTN 084-01

2 participants had an SAE during this study, both during Step 2 (Table below). Neither SAE was considered drug-related by the investigator.

- **Participant** [PPD redacted] **[Verbatim text: Right Ovarian Cyst]:** A participant experienced a Grade 3 AE of PT Ovarian Cyst resulting in hospitalization 3 months and 18 days after the start of CAB and 27 days since the last injection during Step 2 which lasted approximately 14 days. The participant informed the site that she had been admitted to hospital the day prior where she was diagnosed with an ovarian cyst and underwent an ovarian cystectomy. The investigator assessed the event as not related to the study drug. The SAE was reported to be resolved and action taken with study drug was dose not changed.
- **Participant** [PPD redacted] **[Verbatim text: Suicide Attempt]:** A participant experienced a Grade 4 AE of PT Suicide Attempt 4 months, 26 days after the start of CAB and 30 days since the last injection during Step 2. The participant attended for a contraceptive re-supply of depo-provera and informed the site that she took 30 tablets of Truvada in a suicide attempt following a break-up. She "lavaged" at home with water within 2 hours of the overdose. No medical attention was sought, and she was asymptomatic. Urinalysis was reported to be normal; liver and kidney function tests were ordered. Temporary study product hold was initiated per protocol and the participant was scheduled for counselling and a formal mental health assessment. The investigator assessed the event as not related to the study drug and the outcome of the event was resolved. The participant completed her course of CAB LA.

Table 22. HPTN 084-01: Listing of serious adverse events (Safety Population)

Participant ID (30008401-PID)	Step	Preferred term	Action with regard to study drug	Grade	Related[a]
[PPD redacted]	2	Ovarian cyst	Dose not changed	3	No
[PPD redacted]	2	Suicide attempt	Drug interrupted	4	No

Source: Study 213003 CSR Listing 16.140.

- Relationship to study drug as assessed by the investigator.

8.2.2.7. Adverse events of special interest (AESIs)

8.2.2.7.1. Injection site reactions

ISRs have been shown to occur with IM injections due to the method of administration and are known to occur with CAB injections in the HIV treatment program. Overall, injections of CAB PrEP were generally well tolerated in the HPTN 083-01 and HPTN 084-01 populations of adolescents. The nature and severity of ISRs experienced by adolescent participants in these studies are consistent with the known CAB LA safety profile per current product labelling.

In HPTN 083-01, a total of 40 injections were administered to the 9 participants who received injections, and 5 participants (56%) experienced 20 ISRs. All ISRs were considered related to study drug by the investigator. There were no serious ISRs, and no ISRs led to discontinuation of study drug. No participants had ISRs of maximum Grade 3 to 5 intensity. Of the 5 participants who experienced an ISR AESI, all had an outcome of recovered/resolved at the time of data cut-off.

The median duration of ISRs was 4.0 days, and all ISRs (100%) resolved within 7 days. The median (minimum, maximum) time to onset of the first occurrence of ISR AESI was 0.14 (0.1, 0.3) weeks. The time from the start date of Step 2 (Injection Phase) to ISR AESI onset was <2 weeks for all 5 (100%) participants. Overall, the percentage of participants reporting ISRs generally decreased over time.

Table 23. HPTN 083-01: Summary of injection site reactions and characteristics during Step 2 (Injection Population)

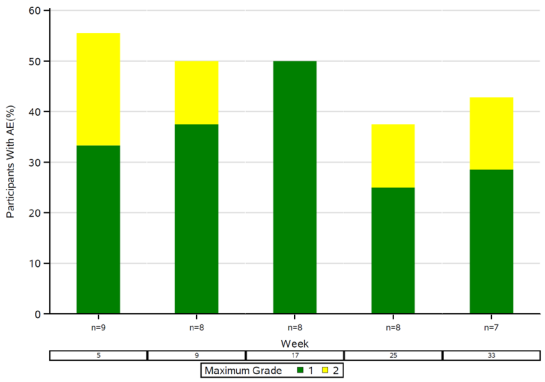
	CAB (N=9)
Number of participants with at least 1 injection, n	9
Total number of ISR AEs, n[a]	20
Number of participants with at least 1 ISR AE, n (%)	5 (56)
Injection site pain	5 (56)
Injection site swelling	1 (11)
Participant-level characteristics, n (%)[b]	
Event characteristics	
Serious	0
Drug-related	5 (56)
Leading to discontinuation	0
Grade 3/4	0
Fatal	0
Number of events per participant, n (%)	
0	4 (44)
1	1 (11)
2	0
3	0
4	1 (11)
5	3 (33)
Maximum grade or intensity, n (%)	
Grade 1	2 (22)
Grade 2	3 (33)
Grade 3	0

	CAB (N=9)
Grade 4	0
Grade 5	0
Event-level characteristics, n (%)[c]	
Event characteristics	
Serious	0
Drug-related	20 (100)
Leading to discontinuation	0
Grade 3/4	0
Fatal	0
Any grade or intensity, n (%)[d]	
Grade 1	14 (70)
Grade 2	6 (30)
Grade 3	0
Grade 4	0
Grade 5	0

Source: Study 213002 CSR Table 3.015, Table 3.866, Table 3.867
Note: All ISRs were considered related to study drug by the investigator.
Note: In Number of ISRs, duplicating ISRs with the same onset date are reported as one unique ISR event.

- An ISR reported more than once by the same participant was counted more than once.
- All participant-level percentages are based on the number of participants with at least 1 injection.
- All event-level percentages are based on the total number of ISRs.
- In "Any grade or intensity", duplicating ISRs with multiple toxicity grades are counted in more than one grade; therefore, the total can be greater than the number of ISRs.

Figure - HPTN 083-01: Plot of incidence of study drug injection site reaction adverse events by visit and intensity in Step 2 (Injection Population)



Source: Study 213002 CSR Figure 3.002
Note: Bars represent percentage of participants with an onset ISR AE relative to the most recent previous IM injection visit.

In HPTN 084-01, a total of 263 injections were administered to the 53 participants who received injections, and 14 participants (26%) experienced 20 ISRs. All ISRs were considered related to study drug by the investigator. There were no serious ISRs, and no ISRs led to discontinuation of study drug. No participants had ISRs of maximum Grade 3 to 5 intensity. Of the 14 participants who experienced an ISR AESI, all had an outcome of recovered/resolved at the time of data cut-off.

The median duration of ISRs was 7.0 days, and most ISRs (80%) resolved within 14 days. The median (minimum, maximum) time to onset of the first occurrence of ISR AESI was 0.21 (0.1, 12.1) weeks. The time from the start date of Step 2 (Injection Phase) to ISR AESI onset was <2 weeks for the majority of the participants (9 [64%]), with lower proportions of participants experiencing ISR AESIs following this period; time to onset was 2-4 weeks for 3 (21%) participants and 5-12 weeks for 2 (14%) participants. The overall reporting of ISRs decreased over time.

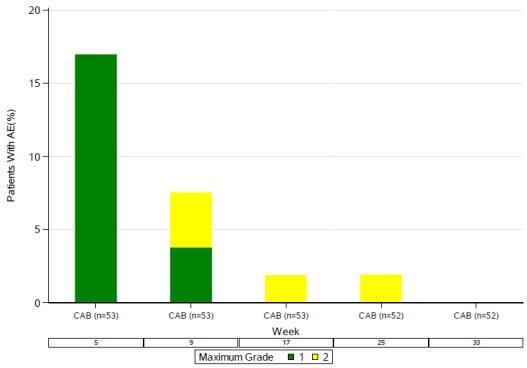
Table 24. HPTN 084-01: Summary of injection site reactions during Step 2 (Injection Population)

	CAB (N=53)
Number of participants with at least 1 injection, n	53
Total number of ISR AEs, n[a]	20
Number of participants with at least one ISR AE	14 (26)
Injection site pain	13 (25)
Injection site induration	2 (4)
Injection site swelling	1 (2)
Participant-level characteristics, n (%)[b]	
Event characteristics	
Serious	0
Drug-related	14 (26)
Leading to discontinuation	0
Grade 3/4	0
Fatal	0
Number of events per participant, n (%)	
0	39 (74)
1	11 (21)
2	2 (4)
≥3	1 (2)
Maximum grade or intensity, n (%)	
Grade 1	11 (21)
Grade 2	3 (6)
Grade 3	0
Grade 4	0
Grade 5	0
Event-level characteristics, n (%)[c]	
Event characteristics	
Serious	0
Drug-related	20 (100)
Leading to discontinuation	0
Grade 3/4	0
Fatal	0
Any grade or intensity, n (%)[d]	
Grade 1	14 (70)
Grade 2	6 (30)
Grade 3	0
Grade 4	0
Grade 5	0

Source: Study 213003 CSR Table 3.003, Table 3.015, Table 3.866, Table 3.867
Note: All ISRs were considered related to study drug by the investigator.
Note: In Number of ISRs, duplicating ISRs with the same onset date are reported as one unique ISR event.

- An ISR reported more than once by the same participant was counted more than once.
- All participant-level percentages are based on the number of participants with at least 1 injection.
- All event-level percentages are based on the total number of ISRs.
- In "Any grade or intensity", duplicating ISRs with multiple toxicity grades are counted in more than one grade; therefore, the total can be greater than the number of ISRs.

Figure - HPTN 084-01: Plot of incidence of study drug injection site reaction adverse events by visit and intensity in Step 2 (Injection Population)



Source: Study 213003 CSR Figure 3.002
Note: Bars represent incidence of onset ISR AEs relative to the most recent IM injection visit.

8.2.2.7.2. Hepatotoxicity

There were no reported events of potential hepatotoxicity AESIs in Step 1 or Step 2 of either HPTN 083-01 or HPTN 084-01.

8.2.2.7.3. Hypersensitivity reactions

There were no reported events of potential hypersensitivity reaction AESIs in Step 1 or Step 2 of either HPTN 083-01 or HPTN 084-01.

8.2.2.7.4. Rash

In HPTN 083-01, 2 participants (22%) each reported a rash AESI event (rash macular and rash) during the study; for both participants, the event was non-serious, Grade 1, and considered not related to study drug by the investigator, and CAB was continued. Specifics are as follows:

- **Participant** [PPD redacted]: developed a non-serious Grade 1 event of rash macular in Step 2, occurring 184 days since the start of CAB that was ongoing and had lasted 214 days at the time of the data cut-off. CAB was continued and the event was considered not related to study drug by the investigator.
- **Participant** [PPD redacted]: developed an event of rash. The Grade 1 event of rash began in Step 2, occurring 57 days since the start of CAB that lasted 36 days, before the event severity was upgraded to Grade 2. The event resolved after 141 days. CAB was continued and the event was considered not related to study drug by the investigator.

In HPTN 084-01, there were no reported events of potential rash AESIs in Step 1 or Step 2 of this study.

8.2.2.7.5. Neuropsychiatric adverse events

No new neuropsychiatric concerns were identified in adolescents compared to the known safety profile observed in the adult PrEP studies (HPTN 083/HPTN 084) and current product labelling. Neuropsychiatric adverse events, including depression, have been reported with CAB in the CAB treatment program in HIV-infected patients and are considered ADRs for CAB.

HPTN 083-01

In HPTN 083-01, there were no reported events of potential Bipolar disorder, Psychosis, or Mood disorders AESIs in Steps 1 or 2 of this study.

Suicidal ideation and behaviour

No participants experienced a Suicidal ideation/behaviour AESI in Step 1 or Step 2; 1 participant experienced 1 event of Suicidal ideation/behaviour AESI (suicidal ideation) in Step 3, which was reported as serious and not related to study drug.

Depression

No Depression AESIs were reported during Steps 1 or 2; 1 participant (2%) experienced a Depression AESI (depression) during Step 3:

- **Participant** [PPD redacted]: developed a non-serious Grade 2 event of depression in Step 3, occurring 399 days since the start of CAB and the participant was recovering/resolving at the data cut-off. CAB was continued and the event was considered not related to study drug by the investigator. This event occurred in the same participant as the SAE of suicidal ideation.

Anxiety

No Anxiety AESIs were reported during Steps 1 or 2; 2 participants experienced an Anxiety AESI during Step 3:

- **Participant** [PPD redacted]: developed a non-serious Grade 2 event of anxiety in Step 3, occurring 353 days since the start of CAB and 190 days since the last CAB LA injection after being dispensed TDF/FTC. The participant was not recovered/resolved at the data cut-off. TDF/FTC was continued and the event was considered not related to study drug by the investigator.
- **Participant** [PPD redacted]: developed a non-serious Grade 2 event of anxiety in Step 3, occurring 330 days since the start of CAB and 42 days since the last CAB LA injection. The participant was recovering/resolving at the data cut-off. CAB was continued and the event was considered not related to study drug by the investigator. This event occurred in the same participant as the SAE of suicidal ideation.

Sleep disorders

2 participants experienced potential Sleep disorder AESIs during the study:

- **Participant** [PPD redacted]: developed a non-serious Grade 1 event of insomnia in Step 1, occurring 8 days since the start of CAB and lasting 15 days. The participant recovered/resolved. CAB was continued and the event was considered not related to study drug by the investigator.
- **Participant** [PPD redacted]: developed a non-serious Grade 1 event of sleep disorder in Step 2, occurring 37 days since the start of CAB and lasting 3 days. The participant recovered/resolved. CAB was continued and the event was considered related to study drug by the investigator.

HPTN 084-01

In HPTN 084-01, there were no reported events of potential Bipolar disorder, Psychosis, Mood disorders, or Sleep disorders AESIs in Steps 1 or 2 of this study.

Suicidal ideation and behaviour

During the study, 1 participant (2%) experienced 1 event of Suicidal ideation/behaviour AESI (suicide attempt, in Step 2), which was reported as serious and not related to study drug.

An additional individual who had transitioned into the HPTN 084 OLE had an AE of suicide attempt.

Depression

During the study, 1 participant (2%) experienced a Depression AESI (depressive symptom, in Step 1)

- **Participant** [PPD redacted] **(depressive symptom) [verbatim text: depressive symptoms]**: a participant experienced a Grade 1 event of depressive symptom during Step 1, 1 day after the first dose of oral CAB (the AE occurred while the participant was taking oral CAB). The duration of the AE was 42 days. The investigator considered this event to be non-serious and related to study drug, and the action taken by the investigator was reported as dose not changed. The participant did not report a history of depression at Baseline. The outcome of the event was reported to be recovered/resolved.

Anxiety

During the study, 1 participant (2%) experienced an Anxiety AESI (stress, in Step 2):

- **Participant** [PPD redacted] **(stress) [verbatim text: stress]**: a participant experienced a Grade 2 event of stress during Step 2, 222 days after the first dose of oral CAB (the AE occurred while the participant was receiving CAB LA). The duration of the AE was 202 days at the time of data cut-off. The investigator considered this event to be non-serious and not related to study drug, and the action taken by the investigator was reported as dose not changed. The participant did not report past history of stress at Baseline. The outcome of the event was reported to be recovering/resolving.

8.2.2.7.6. Seizures and seizure-like events

There were no reported events of potential Seizures and seizure-like AESIs during either HPTN 083-01 or HPTN 084-01.

8.2.2.7.7. Hyperglycaemia and diabetes

As with other INSTIs, there is interest in whether CAB impacts glycaemic control in exposed individuals. Protocol specified blood glucose level measurements did not require collection of blood under fasting conditions. It should be noted that fasting lipid measurements were taken at Baseline and other treatment visits which were scheduled to take place with blood glucose sampling.

HPTN 083-01

In HPTN 083-01, a total of 3 participants (33%) developed 5 events of Hyperglycaemia AESI, all of whom had the PT of hyperglycaemia; 2 participants (22%) had 4 events of hyperglycaemia in Step 2, and 1

participant (11%) had 1 event of hyperglycaemia in Step 1. The frequency of reporting of the hyperglycaemia PT is not corroborated with any laboratory findings relating to blood glucose.

All Hyperglycaemia AESIs had a maximum post-Baseline intensity of Grade 1 (Source: Study 213002 CSR Table 3.004). The time to onset of the first occurrence of a Hyperglycaemia AESI ranged from 26 to 177 days and the duration ranged from 4 to 119 days.

There were no serious or drug-related Hyperglycaemia AESIs and no Hyperglycaemia AESIs led to discontinuation of study drug. The action taken with regard to study drug was dose not changed for all events, and all participants were reported to have recovered.

HPTN 084-01

In HPTN 084-01, a total of 22 participants (40%) developed 31 events of Hyperglycaemia AESI, all of whom had the PT of blood glucose increased. The majority of participants (21 [40%]) had an AE of blood glucose increased in Step 2, and 4 participants (7%) had an AE of blood glucose increased in Step 1. The frequency of reporting of the blood glucose increased PT is not corroborated with the laboratory findings relating to blood glucose.

In Steps 1 and 2, 21/22 (95%) participants had a maximum post-Baseline Grade 1 Hyperglycaemia AESI and 1/22 (5%) participants had a maximum post-Baseline Grade 2 Hyperglycaemia AESI. There were no reports of hyperglycaemia AESIs that were classified as Grade 3 or above (Source: Study 213003 CSR Table 3.688).

The median time to onset (Steps 1 and 2 combined) of the first occurrence of a Hyperglycaemia AESI was 10.07 weeks with a range of 1.4 to 32.3 weeks. The time to onset of the first occurrence for participants who reported at least 1 AESI ranged from <2 weeks in 1 (5%) participant, 2-4 weeks in 3 (14%) participants, 5-12 weeks in 9 (41%) participants, 13-24 weeks in 3 (14%) participants, and 25-48 weeks in 6 (27%) participants. The median duration of the first occurrence of Hyperglycaemia AESIs was 2.79 weeks.

There were no serious or drug-related Hyperglycaemia AESIs and no Hyperglycaemia AESIs led to discontinuation of study drug; all participants were reported to have recovered.

8.2.2.7.8. Weight gain

There were no reported events of potential Weight gain AESIs during either HPTN 083-01 or HPTN 084-01.

8.2.2.7.9. Rhabdomyolysis

HPTN 083-01

There were no reported adverse events consistent with rhabdomyolysis or related AESI terms during the study. Although there were no reported AE consistent with rhabdomyolysis or related AESIs, 1 participant developed a Grade 3 laboratory event of elevated CK, which is described further.

HPTN 084-01

During the study, 1 participant (2%) experienced a Rhabdomyolysis AESI (myalgia, during Step 1):

- **Participant** [PPD redacted] **(myalgia) [verbatim text: left trapezius muscle pain]**: a participant experienced a Grade 2 event of myalgia during Step 1, 7 days after the first dose of oral CAB. The duration of the AE was 7 days. The investigator considered this event to be non-serious and not related

to study drug, and the action taken by the investigator was reported as dose not changed. The outcome of the event was reported to be recovered/resolved.

8.2.2.7.10. Pancreatitis

There were no reported events of potential pancreatitis AESIs during either HPTN 083-01 or HPTN 084-01.

8.2.2.7.11. Impact on creatinine

The potential impact of CAB on renal function was evaluated by examining creatinine and creatinine clearance events. For both HPTN 083-01 and HPTN 084-01, there were no reported events with potential Impact on creatinine AESIs during the study. However, for the AESI term "Impact on creatinine", the pre-specified analysis was expanded to include the additional AE terms "blood creatinine increased" and "creatinine renal clearance decreased", which were not part of the pre-specified AESI for Impact on creatinine. These AE terms are described in the expanded analysis below.

HPTN 083-01

When laboratory findings for creatinine clearance and creatinine values were taken into account, the magnitude of median post-Baseline change of these laboratory values through Week 34 was not clinically relevant. The observed graded laboratory values did not have a clinical impact on any participants, with no associated AEs being reported suggestive of renal toxicity, nor did they result in study drug discontinuation or dose modification.

Blood Creatinine Increased

2 (22%) participants had PT Blood creatinine increased, both occurred during Step 2. Both were considered not drug related by the investigator.

- **Participant** [PPD redacted]: developed a non-serious Grade 2 event of blood creatinine increased in Step 2, occurring 171 days since the start of CAB which lasted 6 days. CAB was continued and the event resolved.
- **Participant** [PPD redacted]: developed a non-serious Grade 1 event of blood creatinine increased in Step 2, occurring 63 days since the start of CAB which lasted 57 days. CAB was continued and the event resolved.

There were no AEs of PT Blood creatinine increased leading to study drug discontinuation.

Creatinine Renal Clearance Decreased

12 events occurred in 6 participants (67%). All were non-serious, Grade 2, and all events were resolving or had resolved apart from 1 event in 1 participant (Participant [PPD redacted]). The event for this participant occurred in Step 2, 187 days since the start of CAB and lasted 533* days (*data censored at the earliest time point as of data cut-off date of 24 October 2022).

There were no AEs of PT creatinine renal clearance decreased that led to study drug discontinuation. Participants in Step 1 and Step 2 with PT creatinine renal clearance decreased had a wide range of times to onset from 11 to 192 days.

No participants had PT creatinine renal clearance decreased that was considered related to study drug by the investigator.

HPTN 084-01

When laboratory findings for creatinine clearance and creatinine values were taken into account, the magnitude of median post-Baseline change of these laboratory values through Week 34 was not clinically relevant. The observed graded laboratory values did not have a clinical impact on any participants, with no associated AEs being reported suggestive of renal toxicity, nor did they result in study drug discontinuation or dose modification. Notably, the majority of lab events for Creatinine 78% (7/9 participants with graded creatinine lab event) were triggered on the DAIDS grading criteria by a change from Baseline with the absolute values remaining within normal limits. Therefore, taken together, these findings do not suggest a significant impact of CAB on creatinine or creatinine clearance in HPTN 084-01.

Blood Creatinine Increased

9 (16%) participants had PT Blood creatinine increased in Steps 1 and 2 (Table below). The majority of participants (6 [11%]) experienced maximum toxicity Grade 2 Blood creatinine increased events. The proportion of participants who experienced Grade 3 events was small. There were no Grade 4 or 5 events.

Table 25. HPTN 084-01: Adverse event of preferred term Blood creatinine increased on CAB by intensity in Steps 1 and 2 (Safety Population)

	CAB (N=55) n (%)
Any Blood creatinine increased AE	9 (16)
Grade 1	1 (2)
Grade 2	6 (11)
Grade 3	2 (4)
Grade 4	0 (0)
Grade 5	0 (0)

Source: Study 213003 CSR Table 3.004

Note: The number of participants is considered only once for the highest toxicity grade.

There were no AEs of PT Blood creatinine increased leading to study drug discontinuation. Participants in Step 1 and Step 2 with PT Blood creatinine increased had a wide range of time to onset from 28 to 232 days. The action taken following PT Blood creatinine increased onset was reported as dose not changed in all.

3/55 (5%) participants were reported as having PT Blood creatinine increased that was considered related to study drug by the investigator, all events were Grade 2 in severity (Table below). The time to onset of these events ranged from 63 to 190 days. The event outcomes in all participants (drug-related AEs) were reported as recovered/resolved. The action taken by the investigator is reported as dose not changed for all participants (drug-related AEs).

Table 26. HPTN 084-01: Drug-related adverse event of preferred term "blood creatinine increased" on CAB by intensity in Steps 1 and 2 (Safety Population)

	CAB (N=55) n (%)
Any drug-related "blood creatinine increased" AE	3 (5)
Grade 1	0 (0)
Grade 2	3 (5)
Grade 3	0 (0)
Grade 4	0 (0)
Grade 5	0 (0)

Source: Study 213003 CSR Table 3.016

Note: The number of participants is considered only once for the highest toxicity grade.

Grade 3 or Higher Unrelated AEs to Study Drug

2 participants had Grade 3 non-serious events of PT Blood creatinine increased considered unrelated to study drug by the investigator. The event outcomes in all participants were reported to be recovered/resolved. The action taken with study drug was reported as dose not changed in both. There were no Grade 4 or 5 events.

Creatinine Renal Clearance Decreased

41 (75%) participants had PT Creatinine renal clearance decreased in Steps 1 and 2 (Table below).

The majority of participants (39 [71%]) had maximum toxicity Grade 2 Creatinine renal clearance decreased events. The proportion of participants with Grade 3 events was small. There were no Grade 4 or 5 events.

Table 27. HPTN 084-01: Adverse event of preferred term "creatinine renal clearance decreased" on CAB by intensity in Steps 1 and 2 (Safety Population)

	CAB (N=55) n (%)
Any "creatinine renal clearance decreased" AE	41 (75)
Grade 1	0 (0)
Grade 2	39 (71)
Grade 3	2 (4)
Grade 4	0 (0)

	CAB (N=55) n (%)
Grade 5	0 (0)

Source: Study 213003 CSR Table 3.004

Note: The number of participants is considered only once for the highest toxicity grade.

There were no AEs of PT Creatinine renal clearance decreased leading to study drug discontinuation. Participants in Step 1 and Step 2 with PT Creatinine renal clearance decreased had a wide range of times to onset from 9 to 262 days. The action taken following PT Creatinine renal clearance decreased onset was reported as dose not changed in all.

12/55 (22%) participants had PT Creatinine renal clearance decreased that was considered related to study drug by the investigator and all were Grade 2 in severity (Table). 6 participants had more than one event. The time to onset of these events ranged from 14 to 190 days. The event outcomes in all participants (drug-related AEs) were reported as recovered/resolved. The action taken by the investigator is reported as dose not changed for all participants.

Of note, 9 out of 41 participants who experienced Creatinine renal clearance decreased AEs on CAB experienced a Creatinine renal clearance decreased AE which occurred after the fifth injection while on Step 2. These events were not considered related to study drug by the investigator. Of note, these participants were provided with TDF/FTC at a safety visit 1 week after their last (5th) injection visit (listed as a concomitant medication) and were instructed to take TDF/FTC at Week 34+7 or Week 33+8.

Table 28. HPTN 084-01: Drug-related adverse event of preferred term "creatinine renal clearance decreased" on CAB by intensity in Steps 1 and 2 (Safety Population)

	CAB (N=55) n (%)
Any drug-related "creatinine renal clearance decreased" AE	12 (22)
Grade 1	0 (0)
Grade 2	12 (22)
Grade 3	0 (0)
Grade 4	0 (0)
Grade 5	0 (0)

Source: Study 213003 CSR Table 3.016

Note: The number of participants is considered only once for the highest toxicity grade.

Grade 3 or Higher Unrelated AEs to Study Drug

2 participants had Grade 3 non-serious AEs of PT creatinine renal clearance decreased that were considered unrelated to study drug by the investigator. The event outcomes in all participants were reported to be recovering/resolving. The action taken with study treatment was reported as dose not changed in both. There were no Grade 4 or 5 events.

8.2.2.8. Other significant adverse events

8.2.2.8.1. Adverse events leading to withdrawal

HPTN 083-01

No participant in HPTN 083-01 had an AE leading to discontinuation of study drug during Steps 1 and 2.

HPTN 084-01

Overall, in HPTN 084-01, 2 participants had AEs leading to discontinuation of study drug, none of which were considered drug related by the investigator (Table below). Both participants discontinued study drug during Step 1 due to non-serious Grade 3 AEs.

Table 29. HPTN 084-01: Listing of adverse events leading to discontinuation of study drug (Safety Population)

Participant ID (30008401-PID)	Step	Preferred term	SAE (Y or N)	Grade	Related[a]
[PPD redacted]	1	Alanine aminotransferase increased	N	3	No
[PPD redacted]	1	Lipase increased	N	3	No

Source: Study 213003 CSR Listing 16.150.

- Relationship to study drug as assessed by the investigator.

8.2.2.8.2. Analysis of adverse events by organ system or syndrome

Analysis of pyrexia and associated terms ("Pyrexia Plus"), sciatica, and other specific musculoskeletal associated terms, and pancreatitis and associated terms ("Pancreatitis Plus") were conducted for the pivotal studies in the CAB PrEP program, based on regulatory interest in both the PrEP and treatment indications, in order to further characterize these occurrences. These topics are being discussed for HPTN 083-01 and HPTN 084-01 using an expanded search and are focusing on events that have not been previously discussed as an AESI In addition, AEs that have not been discussed previously within specific SOCs of interest (hepatobiliary events, neurologic events, gastrointestinal events) and syndromes of vasovagal reactions were also reviewed.

- **Pyrexia Plus**

Pyrexia events and events associated with pyrexia were defined as Pyrexia Plus and included the PTs of pyrexia, influenza like illness, chills, feeling hot, body temperature increased and feeling of body temperature change, fever.

In HPTN 083-01, no participant experienced a Pyrexia Plus event during the study. In HPTN 084-01, 1 participant (2%) experienced a Pyrexia Plus event (pyrexia) during the study:

- **Participant** [PPD redacted] **(pyrexia) [verbatim text: fever of unknown cause]**: a participant experienced a Grade 2 event of pyrexia during Step 2, 182 days after the first dose of oral CAB (the AE occurred while the participant was receiving CAB LA). The duration of the AE was 5 days. The investigator considered this event to be non-serious and not related to study drug, and the action taken by the investigator was reported as dose not changed. The outcome of the event was reported to be recovered/resolved.

- **Pancreatitis and Potentially Associated Events (Pancreatitis Plus)**

Pancreatitis events and events potentially associated with pancreatitis were defined as Pancreatitis Plus and included the PTs of pancreatitis, pancreatic enzymes increased, abdominal pain, abdominal pain upper,

abdominal discomfort, and nausea. In HPTN 083-01, 1 participant experienced a Pancreatitis Plus event (nausea) during the study:

- **Participant** [PPD redacted]: developed a non-serious Grade 1 event of nausea in Step 2, occurring 168 days since the start of CAB and lasting 1 day. The participant/AE recovered/resolved. CAB was continued and the event was considered not related to study drug by the investigator.

In HPTN 084-01, no participant experienced a Pancreatitis Plus event during the study (Source: Study 213003 CSR Table 3.670, Listing 16.120).

- **Sciatica or Musculoskeletal Events**

Musculoskeletal events are defined as PTs of back pain, myalgia, pain in extremity and musculoskeletal pain. In HPTN 083-01, there were no PT events of sciatica or musculoskeletal PTs reported during the study.

In HPTN 084-01, there were no PT events of sciatica reported during the study. For musculoskeletal PTs, 1 event (myalgia) was reported, as previously described.

- **Hepatobiliary Events**

In HPTN 083-01, no participant was reported as having a hepatobiliary event (PT) related to the MedDRA Hepatobiliary SOC during Step 1 or Step 2. In HPTN 084-01, 1 participant was reported as having a hepatobiliary events (PTs) related to the MedDRA Hepatobiliary SOC during Step 1 or Step 2:

- **Participant** [PPD redacted] **[Verbatim text: Raised ALT]**: A participant was reported to have a Grade 3 event of PT Alanine aminotransferase increased during Step 1, 29 days after the first dose of oral CAB. The participant's ALT at Baseline was within normal range (10 IU/L). The duration of the AE was 25 days. The investigator considered the event to be non-serious and not related to the study drug. Study drug was withdrawn, as the participant had met protocol defined stopping criteria. The severity of the event reduced to Grade 1 approximately 3 weeks after CAB discontinuation. The alternative etiology considered in this case was alcohol binge drinking. The outcome of the event was reported to be recovered.

- **Neurologic Events**

As reported in the parent studies HPTN 083 and HPTN 084, an additional review was undertaken of the neurologic events in the Nervous system disorders SOC. Events selected for inclusion were as follows: headache, tension headache, migraine, sinus headache, cluster headache, dizziness, somnolence, and paresthesia. In both HPTN 083-01 and HPTN 084-01, the only AE PTs reported from the Nervous system disorders SOC were Headache and Dizziness.

<u>Headache</u>

In HPTN 083-01, the frequency of AE PT Headache was 2/9 (22%). Of these 2 participants, 4 events of AE PT Headache were reported, none of which the investigator considered was causally related to study product. All were Grade 1 or 2, non-serious, all recovered, and action taken with study drug was reported as dose not changed. 1 of the events occurred during Step 1 in 1 participant, and 3 events occurred during Step 2 in the other participant. The events that occurred during Step 2 had a time to onset since the start of CAB of 56 (Grade 2), 168 (Grade 1), and 253 (Grade 2) days, respectively. Time to onset of the event PT Headache ranged from 7 to 253 days and the duration was 1 to 3.

In HPTN 084-01, the frequency of AE PT Headache was 9/55 (16%). All the events reported were Grade 1-2, non-serious. The action taken with study treatment was reported as dose not changed, and the outcome of the event was recovered/resolved or recovering/resolving. Of these 9 participants, 5 had AE PT

Headache, which the investigator considered was causally related to study product. All were non-serious, all recovered, and action taken with study drug was reported as dose not changed. 3 of the events occurred during Step 1, and 2 events occurred during Step 2. The events (Grade 1) that occurred during Step 2 had a time to onset since the start of CAB of 251 and 70 days, respectively. Time to onset of the event PT Headache ranged from 2 to 251 days and the duration was 1 to 312* days (*data censored at the earliest time point as of data cut-off date of 21 July 2022).

Dizziness

In HPTN 083-01, the frequency of AE PT Dizziness was 1/55 (11%). The single event reported was Grade 1, non-serious, considered not related to study drug by the investigator, the action taken with study drug was reported as dose not changed, and the outcome of the event was recovered/resolved. The event occurred during Step 2. Time to onset of the event was 37 days and the duration was 1 day.

In HPTN 084-01, the frequency of AE PT Dizziness was 4/55 (7%). All the events reported were Grade 1, non-serious although the investigator considered all these events to be related to study drug. All 4 events occurred during Step 1. The action taken with study treatment was reported as dose not changed, and the outcome of the event was recovered/resolved in all. Time to onset of the event ranged from 1 to 2 days and the duration was 2 to 28 days.

For AESI Seizures, please see above. For both studies, there were no reports of PT somnolence during Steps 1 and 2.

- **Gastrointestinal Events**

In HPTN 083-01, AEs in the Gastrointestinal disorders SOC were reported in 2 participants (22%). All GI events occurred in 1 participant (11%) each; diarrhoea in 1 patient and nausea, proctalgia, rectal haemorrhage, and vomiting in the other participant. All GI events occurred during Step 2, were Grade 1 or 2, non-serious, considered not related to study drug by the investigator, the action taken with study drug was reported as dose not changed, and the outcome of the event was recovered/resolved. The time to onset of GI events was 168 to 278 days and the duration ranged from 1 to 8 days.

In HPTN 084-01, Gastrointestinal AEs were reported in 10 participants (18%) (Table 30).

Table 30. HPTN 084-01: Summary of gastrointestinal events during Steps 1 and 2 (Safety Population)

Preferred term	**CAB (N=55) n (%)**
GI disorders	10 (18)
Constipation	3 (5)
Nausea	3 (5)
Abdominal pain	1 (2)
Aphthous ulcer	1 (2)
Dental caries	1 (2)
Enteritis	1 (2)

Preferred term	CAB (N=55) n (%)
Vomiting	1 (2)

Source: Study 213003 CSR Table 3.004

- **Vasovagal Events**

No participants experienced vasovagal events (presyncope and syncope PTs) during either HPTN 083-01 or HPTN 084-01.

8.2.2.9. Adverse events during Step 1 (Oral Phase) (HPTN 083-01 and HPTN-04)

In HPTN 083-01 and HPTN 084-01, Step 1 Oral Phase with CAB was used to assess tolerability and to identify the occurrence of severe AEs that might preclude dosing with CAB LA. Therefore, AEs occurring during the Oral Phase are of interest.

HPTN 083-01

In HPTN 083-01, during Step 1, 8/9 participants (89%) were reported as having any AE, the most common of which were creatinine renal clearance decreased (33%) and blood phosphorus decreased (22%); all others occurred in 1 participant (11%) each. No participants had AEs that were considered related to study drug by the investigator during Step 1. No participants experienced an SAE or AE that led to discontinuation of study drug during Step 1. There were no Grade 3 or higher AEs reported in Step 1.

HPTN 084-01

In HPTN 084-01, during Step 1, 51/55 participants (93%) were reported as having any AE, the most common of which were creatinine renal clearance decreased (29%), amylase increased (25%), and lipase increased (20%). 20/55 participants (36%) had AEs that were considered related to study drug by the investigator, the most common of which were amylase increased (7%), creatinine renal clearance decreased (7%), and dizziness (7%). There were no SAEs during Step 1. Two participants (4%) experienced AEs that led to discontinuation of study drug during Step 1 (PTs of ALT increased and lipase increased). Grade 3 or higher AEs of amylase increased, lipase increased, and alanine aminotransferase increased were reported for 1 participant (2%) each, none of which were considered related to study drug by the investigator. There were no Grade 4 or 5 AEs reported during Step 1.

8.2.2.10. Adverse events after Step 2(HPTN 083-01 and HPTN-04)

HPTN 083-01

In HPTN 083-01, after Step 2, participants in Step 3 could receive CAB LA or TDF/FTC. A total of 6 participants received CAB LA during Step 3 and 5 (83%) experienced AEs (Table 31). The most common AE during Step 3 while on CAB LA was injection site pain (3 participants [50%]); all other AEs during Step 3 were reported in 1 participant each.

Table 31. HPTN 083-01: Summary of all adverse events in Step 3 while on CAB LA (Safety Population)

Preferred term	CAB (N=6) n (%)
Number of participants with any AE	5 (83)
Injection site pain	3 (50)
Anxiety	1 (17)
Blood glucose decreased	1 (17)
Depression	1 (17)
Ear infection	1 (17)
Injection site swelling	1 (17)
Lipase increased	1 (17)
Suicidal ideation	1 (17)
Uncoded	1 (17)
Upper respiratory tract infection	1 (17)

Source: Study 213002 CSR Table 3.030

HPTN 084-01

In HPTN 084-01, after Step 2, participants who entered Step 3 or the pregnancy schedule received TDF/FTC; additionally, participants were offered the opportunity to join the HPTN 084 OLE study instead of beginning or continuing with Step 3. Thus, there are no AE findings to report for this study from participants receiving CAB in HPTN 084-01 Step 3 or the pregnancy schedule (because only TDF/FTC was administered).

Assessor's comments

Overall, AE data from the HPTN 083-01 and HPTN 084-01 studies in adolescents did not show any new emergent safety concerns when compared with the known safety profile of CAB PrEP for adults (HPTN 083 and HPTN 084 studies in adults). CAB PrEP in adolescents was in general well-tolerated.

In both studies, all participants reported at least one AE during Step 1 and/or Step 2, the majority of which were considered by the investigator to be drug-related. Across the studies, there were no drug-related or fatal SAEs and no drug-related AEs or ISRs led to discontinuation of study drug.

In HPTN 083-01, AEs in Steps 1 and 2 were reported most frequently from either the Investigations SOC (9 [100%] participants) or General disorders and administration site conditions SOC (5 [56%] participants). The proportion of participants who had events considered drug-related by the investigator was 56% (n=5). The most frequently reported drug-related AE was injection site pain (n=5). In HPTN 084-01, AEs in Steps 1 and 2 were reported most frequently from either the Investigations SOC (55 [100%] participants) or Infections and infestations SOC (29 [53%] participants). The proportion of participants who had events considered drug-related by the investigator was 37 (67%). The most frequently reported drug-related AE was injection site pain (n=13; 24%).

In study HPTN 083-01, no participants had an SAE during Steps 1 or 2 but one participant had an SAE of suicidal ideation during Step 3 (participant [PPD redacted]), though was not drug-related as assessed by the investigator. This is agreed, since other factors could had played a role (co-medication). Another suicide attempted occurred during step 2 in study HPTN 084-01 (participant [PPD redacted]) and was assessed as not drug-related by the investigator, which given the narrative provided, is agreed. Nevertheless, 'suicide ideation and attempt' in adolescents are a special warning in the section 4.4 of the SmPC and are labelled in the section 4.8 with a frequency of uncommon.

In studies HPTN 083-01 or HPTN 084-01, there were no unexpected safety findings related to identified CAB-related risks of hepatotoxicity, hypersensitivity reactions, seizures and seizure-like events, weight gain, or pancreatitis.

8.2.3. Clinical Laboratory Evaluations (HPTN 083-01 and HPTN-04)

8.2.3.1. Clinical chemistry

Most emergent clinical chemistry toxicities were of Grade 1 or Grade 2 intensity. There were few emergent clinical chemistry toxicities of Grade 3 (Table below), and no Grade 4 shifts were reported.

Table 32. Maximum Grade 3 post-Baseline clinical chemistry parameter shifts observed in studies HPTN 083-01 and HPTN 084-01 (Safety Population)

Laboratory parameter Grade	HPTN 083-01 CAB (N=9) n (%)	HPTN 084-01 CAB (N=55) n (%)
Alanine aminotransferase (IU/L)	0	1 (2)[a]
Amylase (IU/L)	0	2 (4)
Creatine kinase (IU/L)	1 (13)[b]	1 (2)[c]
Creatine (µmol/L)	0	2 (4)
Creatinine clearance (mL/min)	0	2 (4)
Lipase (IU/L)	1 (11)	1 (2)

Source: Study 213002 CSR Table 4.021, Study 213002 CSR Table 4.021
Note: Includes events Grade 1 or higher at Baseline
- There were 54 participants with values provided for ALT in Study HPTN 084-01
- There were 8 participants with values provided for creatine kinase in Study HPTN 083-01
- Represents 1 participant from Study HPTN 084-01 with Grade 4 CK abnormality at Baseline reduced in severity to Grade 3

Clinically relevant chemistry laboratory findings are summarized in the sections below. There were no clinically relevant findings in either study with regards to glucose or lipid parameters.

8.2.3.1.1. Creatine kinase

HPTN 083-01

In HPTN 083-01, during Steps 1 and 2, post-Baseline CK increases occurred in 1 (13%) participant. 1 (13%) participant had maximum post-Baseline CK increase that was Grade 3. No participants had a maximum post-Baseline CK increase above Grade 3 in severity. The median (Q1, Q3) CK level at Baseline was 134 (90, 215) IU/L (based on n=9). The median change from Baseline at Week 5 and at Week 34, respectively, was 12 (-80, 16) IU/L (based on n=7) and -9.5 (-82, -1) IU/L (based on n=6).

- **Participant** [PPD redacted] developed two non-serious laboratory events reported as AEs of elevated CK (Blood creatine phosphokinase increased), the first occurred in Step 2, 176 days since start of CAB PrEP and 1 days since last injection. The event was Grade 1, lasted 4 days, resolved and was not considered related by the investigator. This participant also had a Grade 1 non-serious AST occurring on the same day lasting 4 days which resolved and was not considered related by the investigator. Of note, 4 weeks earlier, the participant sustained a 'limb injury'. The second non-serious event of elevated CK (Blood creatine phosphokinase increased), occurred in Step 2, 185 days since start of CAB PrEP and 10 days since last injection. The event was Grade 3, lasted 7 days, resolved, and was not considered related by the investigator. This was also accompanied by a non-serious Grade 1 AST increase lasting 7 days, which resolved and was not considered related by the investigator. 6 days after this, the same participant developed a non-serious Grade 2 event of decreased creatinine clearance lasting 206 days, which was not considered related by the investigator and resolved.

HPTN 084-01

In Steps 1 and 2 of HPTN 084-01, post-Baseline CK increases (Grade 1 to 4) occurred in 7 (13%) participants. 13% of participants had maximum post-Baseline CK increases that were either Grade 1 or Grade 2. No participants had a maximum post-Baseline CK increase above Grade 3 in severity. 1 participant with Grade 4 CK abnormality at Baseline reduced in severity to Grade 3. The median (Q1, Q3) creatine kinase level at Baseline was 134 (109, 169) IU/L (based on n=55). The median change from Baseline at Week 5 and at Week 34, respectively, was 2 (-14, 21) IU/L (based on n=53) and -4 (-27, 16) IU/L (based on n=51).

8.2.3.1.2. Lipase

HPTN 083-01

In HPTN 083-01, during Steps 1 and 2, post-Baseline lipase elevations (Grade 1 to 3) occurred in 1 (11%) participant. 1 (11%) of participants had maximum post-Baseline lipase elevations that were Grade 3. No participants had a maximum post-Baseline lipase elevation above Grade 3 in severity.

The median (Q1, Q3) lipase value at Baseline was 18.0 (15.0, 22.0) IU/L. The median change from Baseline at Week 5 and at Week 34, respectively, was 2.5 (1.5, 6.0) IU/L (based on n=8) and 3.0 (0.0, 8.0) IU/L (based on n=7).

There were no AEs potentially associated with pancreatitis during this study.

However, a Grade 3 non-serious AE of Lipase increased developed in Participant [PPD redacted] in Step 2 occurring 137 days since first dose of CAB and 13 days since the last injection, lasting 15 days in duration. This event was not considered related to study drug by the investigator and resolved. This was also accompanied by a non-serious Grade 1 AE of Amylase increased occurring on the same day, lasting the same duration, not considered related to study drug by the investigator and also resolved. There were no AEs occurring proximal to this date to explain this increase. There was no report of abdominal pain or other symptoms that could be associated with pancreatitis.

HPTN 084-01

In Steps 1 and 2 of HPTN 084-01, post-Baseline lipase elevations (Grade 1 to 4) occurred in 21 (38%) participants. 20 (36%) participants had lipase elevations that were either Grade 1 or Grade 2. 1 (2%) participant had a maximum post-Baseline lipase elevation of Grade 3 (from Grade 2 at Baseline). There were no Grade 4 lipase elevations.

1 participant with Grade 2 lipase abnormality at Baseline reduced in severity to Grade 1.

The median (Q1, Q3) lipase value at Baseline was 26.0 (21.0, 34.0) IU/L. At Week 5 and Week 34, respectively, the median (Q1, Q3) lipase values were 28.0 (23.0, 42.0) IU/L and 27.0 (23.0, 34.0) IU/L (Source: Study 213003 CSR Table 4.004). The median change from Baseline at Week 5 and at Week 34, respectively, was 4.0 (0.0, 8.0) IU/L (based on n=53) and 2.0 (-2.0, 6.0) IU/L (based on n=50).

There were no AEs potentially associated with pancreatitis during this study.

8.2.3.1.3. Liver chemistry

HPTN 083-01

In HPTN 083-01, during Steps 1 and 2, all treatment-emergent liver laboratory parameters abnormalities were Grade 1 or 2; there were no Grade 3 or 4 elevations (Table below). There were no results that qualified as Grade 1 or higher for bilirubin or alkaline phosphatase.

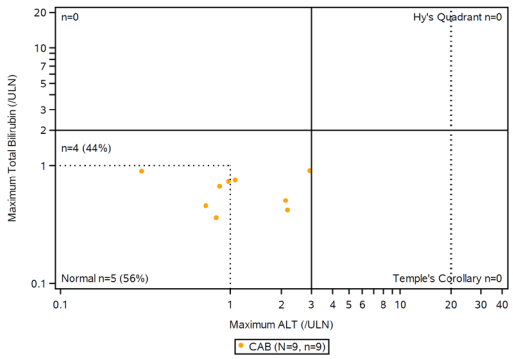
Table 33. HPTN 083-01: Liver function test parameters by intensity from Baseline to maximum post Baseline for Steps 1 and 2 (Safety Population)

Laboratory parameter **Grade**	**CAB (N=9)** **n (%)**
Alanine aminotransferase (IU/L)	
Grade 1	2 (22)
Grade 2	1 (11)
Grade 3	0
Grade 4	0
Aspartate aminotransferase (IU/L)	
Grade 1	2 (22)
Grade 2	0
Grade 3	0
Grade 4	0
Bilirubin (µmol/L)	
Grade 1	0
Grade 2	0
Grade 3	0
Grade 4	0
Alkaline phosphatase (IU/L)	
Grade 1	0
Grade 2	0
Grade 3	0
Grade 4	0

Source: Study 213002 CSR Table 4.021
Note: Includes events Grade 1 or higher at Baseline

During Steps 1 and 2, no participants met any hepatobiliary abnormality criteria. Figure presents a plot of maximum ALT at any time vs. maximum total bilirubin values at any time during Steps 1 and 2. There were no participants who met both ALT >3 × ULN and total bilirubin >2 × ULN criteria.

HPTN 083-01: Scatter plot of maximum total bilirubin vs maximum ALT (Steps 1 and 2) – eDISH



Source: Study 213002 CSR Figure 4.003
Note: Reference lines represent 1 × and 2 × ULN for Total Bilirubin and 1 ×, 3 ×, 20 × ULN for ALT. Maximum ALT (/ULN) and maximum Total Bilirubin (/ULN) during Steps 1 and 2.
Note: Data recorded as Step 1 or 2 visits but after treatment discontinuation are excluded. The percentages are based on the n = number of participants with post-Baseline Bilirubin and ALT value.
Note: Participants without a post-Baseline Bilirubin and/or ALT value are excluded from the analysis.

HPTN 084-01

During Steps 1 and 2 of HPTN 084-01, maximum intensity of Grade 3 or 4 treatment-emergent liver laboratory parameters abnormality occurred in 1 participant (Grade 3 ALT increase) (Table below). The majority of elevations were Grade 1 or 2.

Table 34. HPTN 084-01: Liver function test parameters by intensity from Baseline to maximum post Baseline for Steps 1 and 2 (Safety Population)

Laboratory parameter **Grade**	**CAB (N=55)** **n (%)**
Alanine aminotransferase (IU/L)	
Grade 1	7 (13)
Grade 2	0
Grade 3	1 (2)
Grade 4	0
Aspartate aminotransferase (IU/L)	
Grade 1	5 (9)
Grade 2	0
Grade 3	0
Grade 4	0
Bilirubin (µmol/L)	
Grade 1	5 (9)
Grade 2	5 (9)
Grade 3	0
Grade 4	0
Alkaline phosphatase (IU/L)	
Grade 1	12 (22)
Grade 2	2 (4)
Grade 3	0
Grade 4	0

Source: Study 213003 CSR Table 4.021
Note: Includes events Grade 1 or higher at Baseline.

During Steps 1 and 2, there was 1 participant with ALT elevation ≥3 × ULN (this was ALT elevation ≥5 and <10 × ULN).

Table 35. HPTN 084-01: Summary of participants meeting hepatobiliary abnormality criteria during Steps 1 and 2 (Safety Population)

Laboratory criterion	CAB (N=55) n (%)
N	54
Hepatocellular injury[a]	1 (2)
Hepatocellular injury[a] and BIL ≥2 × ULN[b,c]	0
N	54
ALT ≥3 × ULN	1 (2)[d]
ALT ≥5 × ULN	1 (2)[d]
ALT ≥8 × ULN	0
ALT ≥10 × ULN	0
ALT ≥20 × ULN	0

Source: Study 213003 CSR Table 4.026
Note: Participants may be counted in more than one category.
- Hepatocellular injury is defined as ([ALT/ALT ULN]/[ALP/ALP ULN]) ≥5 and ALT ≥3 × ULN. ALT and ALP values must occur on the same day.
- If direct bilirubin is available (on the same date as Total Bilirubin), then direct bilirubin as a portion of total bilirubin must be ≥35% when total bilirubin is ≥2 × ULN, in order to satisfy the criteria.
- Bilirubin value is on or up to 28 days after ALT value.
- The same participant is represented by both the ALT ≥3 × ULN and ALT ≥5 × ULN rows.

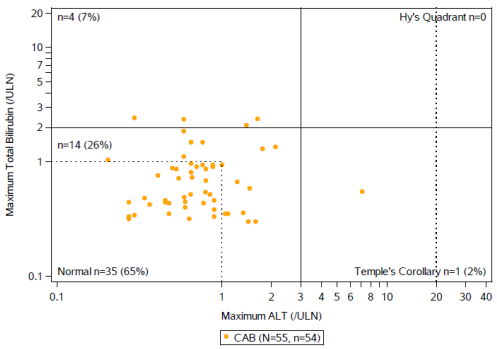
Table 36. HPTN 084-01: Summary of participants with ALT greater than or equal to 3 × ULN during Steps 1 and 2 (Safety Population)

Hepatobiliary criteria	CAB (N=55) n (%)
N	54
ALT ≥3 × ULN to <5 × ULN	0
ALT ≥5 × ULN to <10 × ULN	1 (2)
ALT ≥10 × ULN to <20 × ULN	0
ALT ≥20 × ULN	0

Source: Study 213003 CSR Table 4.026

Figure presents a plot of maximum ALT at any time vs. maximum total bilirubin values at any time during Steps 1 and 2. There were no participants who met both ALT >3 × ULN and total bilirubin >2 × ULN criteria.

Figure - HPTN 084-01: Scatter plot of maximum total bilirubin vs maximum ALT (Steps 1 and 2) – eDISH



Source: Study 213003 CSR Figure 4.003
Note: Reference lines represent 1 × and 2 × ULN for Total Bilirubin and 1 ×, 3 ×, 20 × ULN for ALT. Maximum ALT (/ULN) and maximum Total Bilirubin (/ULN) during Steps 1 and 2.
Note: Data recorded as Step 1 or 2 visits but after treatment discontinuation are excluded. The percentages are based on the n = number of participants with post-Baseline Bilirubin and ALT value.
Note: Participants without a post-Baseline Bilirubin and/or ALT value are excluded from the analysis

8.2.3.1.4. Creatinine and creatinine clearance

HPTN 083-01

Creatinine

In HPTN 083-01, during Steps 1 and 2, maximum post-Baseline creatinine changes occurred in 2 (22%) participants, and all these creatinine elevations were of maximum Grade 1 or 2 intensity. The median (Q1, Q3) creatinine level at Baseline was 76.00 (69.0, 87.50) µmol/L (based on n=9). The median change from Baseline at Week 5 and at Week 34, respectively, was -0.90 (-5.30, 2.70) µmol/L (based on n=9) and -6.20 (-13.30, 4.40) µmol/L (based on n=7).

Creatinine Clearance

In Step 1 and Step 2, 4 (44%) participants who had no grade creatinine clearance at baseline developed a maximum post-Baseline creatinine clearance of Grade 2. 4 (44%) participants had creatinine clearance of Grade 2 in severity at Baseline, which remained unchanged. None had creatinine clearance of Grade 3 and 4 in severity. The median (Q1, Q3) creatinine clearance at Baseline was 93.0 (77.0, 94.0) mL/min (based on n=9). The median change from Baseline at Week 5 and at Week 34, respectively, was 3.0 (-3.0, 8.0) mL/min (based on n=9) and 8.0 (-6.0, 10.0) mL/min (based on n=7).

HPTN 084-01

Creatinine

In HPTN 084-01, during Steps 1 and 2, maximum post-Baseline creatinine changes occurred in 9 (16%) participants. 7 (13%) participants had creatinine elevations that were of maximum Grade 1 or 2 intensity, and 2 (4%) had creatinine elevations that were of maximum Grade 3 intensity. None had Grade 4 elevations. The median (Q1, Q3) creatinine level at Baseline was 53.00 (47.70, 58.90) µmol/L (based on n=55). The median change from Baseline at Week 5 and at Week 34, respectively, was 2.40 (-2.20, 5.20) µmol/L (based on n=53) and 4.50 (0, 8.40) µmol/L (based on n=51).

16% [9/55] participants developed 20 events of graded creatinine lab abnormalities during Step 1 and Step 2. Of these, 2 participants had laboratory events triggered on the DAIDS grading criteria due to the absolute value being above the ULN and 7 participants had lab events which triggered on the DAIDS grading criteria due to change from Baseline (i.e., the actual creatinine lab values were within normal limits). Most participants developed graded laboratory events of creatinine elevation of Grade 1 or 2 in severity.

2 Grade 3 lab events occurred in 1 participant (Participant [PPD redacted]; see CrCl section for details), who notably had an AE of influenza occurring proximal to the Grade 3 laboratory events that resolved, and 1 Grade 3 event in another (Participant [PPD redacted]; see below for details). Of note, all 3 events were triggered due to change from Baseline.

Creatinine Clearance

In Step 1 and Step 2, maximum post-Baseline creatinine clearance changes occurred in 37 (68%) participants. 35 (64%) participants had creatinine clearance of Grade 2 and 2 (4%) participants had creatinine clearance of Grade 3 in severity. None had Grade 4 creatinine elevations. 5 (9%) participants with creatinine clearance of Grade 2 in severity at Baseline remained unchanged. The median (Q1, Q3) creatinine clearance at Baseline was 110.0 (96.0, 119.0) mL/min (based on n=55). The median change from Baseline at Week 5 and at Week 34, respectively, was -4.0 (-11.0, 5.0) mL/min (based on n=53) and -7.0 (-16.0, 0.0) IU/L (based on n=51).

On further analysis of the laboratory data, 44 participants 80% [44/55] developed 207 graded lab events of CrCl in Step 1 and Step 2.

There were 2 participants who experienced Grade 3 decreases in CrCl during Step 1 and Step 2:

- **Participant** [PPD redacted], with a normal baseline CrCl, developed 6 Grade 3 CrCl lab events that were triggered due to change from Baseline and absolute value. At a second Week 34 visit, a Grade 2 lab event of CrCl was also triggered due to change from Baseline. This participant also had 2 Grade 3 increased creatinine lab events which subsequently triggered by change from Baseline, but the absolute value remained within the normal range. Additionally, this participant developed 3 AEs of Creatinine renal clearance decreased (1 Grade 3, 2 Grade 2), and 1 Grade 3 event of Blood creatinine increased, all of which were non-serious, not considered related to CAB by the investigator, and did not result in discontinuation. All AEs apart from 1 Grade 2 event were resolved/resolving. Notably, this participant had 2 AEs of Influenza proximal to their Week 18 and Week 34 visits where they had a Grade 3 lab event of CrCl and Grade 3 lab event of decreased CrCl and Cr increased.
- **Participant** [PPD redacted] had 1 Grade 3 CrCl lab event which triggered on the DAIDS grading criteria due to change from Baseline; however, the CrCl remained above 90 mL/min. Additionally, 1 Grade 3 increased creatinine lab event developed which was triggered by change from Baseline at a Week 26 visit and resolved at a second Week 26 visit. This participant also had a Grade 3 non-serious AE of Creatinine renal clearance decreased which was resolving, considered not related to CAB by the investigator, and did not result in discontinuation.

At the end of the Step 2 (Injection Phase) at Week 34, a total of 22 participants had graded lab events of creatinine clearance which were predominantly Grade 2. Of these:

- In 7 participants, the CrCl grading was triggered due to absolute value but not change from Baseline. Of note, 3 of these participants had lab events of CrCl that were triggering at Baseline/enrollment and the other 4 had CrCl values within normal limits at enrollment.
- In 4 participants, the CrCl grading was triggered by absolute value and change from Baseline.
- In 12 participants, the laboratory grading for CrCl was triggered by change from Baseline but not absolute value.

For the 4 participants where CrCl grading was triggered by absolute value and change from Baseline:

- **Participant** [PPD redacted] see above for more information.
- **Participant** [PPD redacted] had a baseline CrCl of 98 mL/min but grading was triggered due to a decrease/change from Baseline of 16.33% and an absolute value of 82 mL/min at Week 34. Of note, proximal to the Week 5 visit, this participant had an upper respiratory tract infection. There were no graded lab events for creatinine at Week 34; however, this participant had 3 non-serious Grade 2 AEs of Creatinine renal clearance decreased (1 in Step 1 and the other 2 in Step 2). The first 2 events were considered related to CAB by the investigator and resolved; however, the third event was not considered related to CAB by the investigator and was not reported to have resolved at the time of the data cut-off date. These events did not result in discontinuation.
- **Participant** [PPD redacted] had a Baseline CrCl of 102 mL/min but grading was triggered due to a decrease/change from Baseline of 11.76% and an absolute value of 90 mL/min at Week 34. There were no graded lab events for Creatinine at Week 34; however, this participant also had 2 non-serious Grade 2 AEs of Creatinine renal clearance decreased (1 in Step 1 and the other in Step 2), and 3 non-serious

AEs of Proteinuria in Step 2 (1 Grade 3 and 2 Grade 2), which were not considered related to CAB by the investigator, resolved, and did not result in discontinuation.

- **Participant** [PPD redacted] had a Baseline CrCl of 111 mL/min and grading was triggered due to a decrease/change from Baseline of 20.72% and an absolute value of 88 mL/min at Week 34. There were no graded lab events for Creatinine at Week 34; however, this participant had 2 non-serious Grade 2 AEs of Creatinine renal clearance decreased occurring in Step 2 which resolved and did not result in study discontinuation. The first event was considered related to CAB by the investigator although the second event was not considered related to CAB by the investigator.

Overall, in Step 1 and Step 2, while a majority of participants 80% [44/55] developed lab events for Creatinine clearance (1 Participant with Grade 1, 42 participants with Grade 2 and 2 participants with Grade 3 events), only 16% (9/55 participants) developed graded lab events for Creatinine (1 participant with Grade 1, 8 participants with Grade 2 and 2 participants Grade 3 events). The majority of lab events for Creatinine 78% (7/9 participants with graded creatinine lab event) were triggered on the DAIDS grading criteria by a change from Baseline with the absolute values remaining within normal limits.

Although AEs of Creatinine renal clearance decreased and Blood creatinine increased were reported for some of the participants, no other AEs were reported that were associated with renal toxicity. Proteinuria was reported in 8 participants and all events were non-serious, all resolved, and did not lead to discontinuation. Only two of these events were considered related to CAB by the investigator.

Of note, the method of grading CrCl and creatinine lab values may be relevant to these observations. Specifically, the DAIDS grading table requires grading of creatinine and creatinine clearance values based on both the actual laboratory-measured value and the change from Baseline, with the higher of the 2 grades assigned as the reported grade for creatinine or creatinine clearance lab events

8.2.3.1.5. Glucose

In both HPTN 083-01 and HPTN 084-01, there were no clinically relevant post-Baseline changes for fasting and non-fasting glucose during the course of the study.

8.2.3.1.6. Lipid parameters

In both HPTN 083-01 and HPTN 084-01, there were no clinically relevant post-Baseline changes for each of the NCEP lipid categories (cholesterol, LDL cholesterol, triglycerides, HDL, and cholesterol to HDL ratio) during the course of the study.

8.2.3.1.7. Clinical haematology

In HPTN 083-01, there were no reported maximum post-Baseline haematology abnormalities for haemoglobin, leukocytes, lymphocytes, or neutrophils. One participant, who had a maximum post-Baseline Grade 1 platelet abnormality, also had a Grade 1 platelet abnormality at Baseline. There were no Grade 2, 3, or 4 abnormalities reported. In HPTN 084-01, 1 participant had a Grade 3 abnormality for any of these parameters (neutrophils). There were no Grade 4 abnormalities.

8.2.3.1.8. Urinalysis

Urine glucose and urine protein were evaluated during HPTN 083-01 and HPTN 084-01. In both studies, no clinically meaningful trends were noted over the course of the study for either urine glucose or urine protein.

Assessor's comments

Laboratory findings did not show any new relevant clinical safety concerns when compared with CAB PrEP studies for adults. Most emergent clinical chemistry toxicities were of Grade 1 or Grade 2 intensity. There were few emergent clinical chemistry toxicities of Grade 3, and no Grade 4 shifts were reported. In what concerns to clinical hematology no new safety concerns have emerged. In both HPTN 083-01 and HPTN 084-01 studies, no clinically meaningful trends were noted over the course of the study for either urine glucose or urine protein.

8.2.4. Vital signs, physical findings, and other observations related to safety(HPTN 083-01 and HPTN-04)

8.2.4.1. Vital signs

For both HPTN 083-01 and HPTN 084-01, changes in vital signs (including blood pressure and pulse) from Baseline over time were not considered clinically significant.

8.2.4.2. Weight and body mass index

Weight gain was to be expected for the growing adolescent populations during the HPTN 083-01 and HPTN 084-01 studies. As anticipated, there were increases in median weight and median BMI from Baseline to Week 34 in both studies. There were no reported events of potential Weight gain AESIs during either study.

8.2.4.3. Acceptability and tolerability

In HPTN 083-01, analyses showed that CAB LA injections were well tolerated. 1 participant (11%) discontinued the injection treatment prematurely due to intolerability of injection or burden of study procedures. Administration of CAB LA was considered acceptable with 7 of 9 (78%) of participants who entered the Injection Phase receiving all scheduled injections and 67% of participants who would consider using injectable CAB LA (with or without condoms) for HIV prevention in the future.

In HPTN 084-01, analyses showed that CAB LA injections were well tolerated. No participants discontinued the injection treatment prematurely due to intolerability of injection or burden of study procedures. Administration of CAB LA was considered acceptable with 100% of participants who entered the Injection Phase receiving all scheduled injections and 62% of participants who would consider using injectable CAB LA (with or without condoms) for HIV prevention in the future.

Assessor's comments

In both studies, changes in vital signs, weight and body mass index did not show any new safety concerns. In what regards to acceptability and tolerability, study findings are acceptable.

8.2.5. Safety in special groups and situations (HPTN 083-01 and HPTN-04)

Intrinsic factors

Sex, age, and race

No pre-specified analysis has been done on sex (at birth), age, and race in the CAB PrEP studies, HPTN 083-01 and HPTN 084-01.

Extrinsic factors

There are no new safety data to report regarding extrinsic factors from Studies HPTN 083-01 and HPTN 084-01.

Drug interactions

There are no new data to report regarding drug interactions from Studies HPTN 083-01 and HPTN 084-01.

Use in pregnancy and lactation

The safety of CAB PrEP (oral or LA) during human pregnancy and breastfeeding has not been established. HPTN 083-01 was conducted in participants assigned male sex at birth, so pregnancies were not applicable for that study. In HPTN 084-01, 1 participant had a confirmed pregnancy during this study. No AEs were reported during the confirmed pregnancy, and the outcome was a spontaneous abortion at less than 20 weeks with no foetal or infant congenital abnormalities noted.

Overdose

There are no new safety data to report regarding potential for overdose from Studies HPTN 083-01 and HPTN 084-01.

Drug abuse

There are no new safety data to report regarding potential for drug abuse from Studies HPTN 083-01 and HPTN 084-01.

Withdrawal and rebound

There are no new safety data to report regarding potential for withdrawal or rebound from Studies HPTN 083-01 and HPTN 084-01.

Effects on ability to drive or operate machinery or impairment of mental ability

There are no new safety data to report regarding effects on ability to drive or operate machinery or impairment of mental ability from Studies HPTN 083-01 and HPTN 084-01.

Assessor's comments

The information provided for safety in special groups and situations is acknowledged. Of note to be mentioned was a pregnancy in study HPTN 084-01. The MAH stated that no AEs were reported during the confirmed pregnancy, and the outcome was a spontaneous abortion at less than 20 weeks with no foetal or infant congenital abnormalities noted.

The safety of CAB PrEP (oral or LA) during human pregnancy and breastfeeding has not been established. 'Use in pregnancy and breastfeeding' is a safety concern in the RMP (missing information) and all the reported pregnancies are being monitored and characterized by the MAH. Moreover the "study 215325: The Antiretroviral Pregnancy Registry (APR) to monitor CAB LA PrEP use in Pregnancy" is a planned PASS category study in the RMP.

8.2.6. Sexual risk behaviour (HPTN 083-01 and HPTN-04)

A secondary endpoint of both HPTN 083-01 and HPTN 084-01 was the change from enrolment of self-reported sexual behaviour during the oral and injection phases. In both of these adolescent PrEP studies, there was no evidence of an increase in sexual risk behaviour over time.

Assessor's comments

Sexual risk behaviour was defined as a secondary endpoint for the studies conducted. Overall, across both studies, there was no evidence of an increase in sexual risk behavior overtime with CAB LA as PrEP in the adolescent population during the oral and injection phases.

8.2.7. Supportive study: Safety in adolescents living with HIV from Study 208580

The safety of CAB used in adolescents (age 12 to <18 years of age and weighing at least 35 kg) for PrEP is informed by the safety data from Cohort 1C of Study 208580, which enrolled 30 participants who received CAB in addition to cART. Findings through Week 16 are available for this cohort. An overall summary of AEs is provided in the Table below.

Table 37. Study 208580: Overview summary of adverse events (Cohort 1 All Treated Population – Week 16)

AE parameter	Cohort 1C Q4W (N=8) n (%)	Cohort 1C Q8W (N=22) n (%)	Cohort 1C total (N=30) n (%)
Any AE	**7 (87.5)**	**19 (86.4)**	**26 (86.7)**
Any AE excluding ISRs	7 (87.5)	19 (86.4)	26 (86.7)
Any ISR AE	5 (62.5)	4 (18.2)	9 (30.0)
Any AE ≥Grade 3[a]	3 (37.5)	4 (18.2)	7 (23.3)
Any drug-related AE[b]	5 (62.5)	4 (18.2)	9 (30.0)
Any drug-related AE[b] excluding ISRs	2 (25.0)	1 (4.5)	3 (10.0)
Any drug-related AE[b] ≥Grade 3[a]	1 (12.5)	0	1 (3.3)
Any drug-related AE[b] causing permanent treatment discontinuation	0	0	0
Any SAE	0	1 (4.5)	1 (3.3)
Any drug-related SAE[b]	0	0	0
Any fatal SAE	0	0	0

Source: Study Report TMF-16153855 in-text Table 12.
- Grade 3 = Severe, 4 = Potentially Life-Threatening; no Grade 5 AEs were reported.
- Relatedness of AEs was determined by the sites.

The most frequently reported AEs through Week 16 in Cohort 1C were injection site pain, cough, blood pressure increased, hypertension, oropharyngeal pain, and nasal congestion.

Most participants with AEs assessed as related to study intervention in Cohort 1C reported ISRs. Other than ISRs, each AE PT assessed as related to study intervention were reported by single participants within Cohort 1C. All Cohort 1C non-ISR AEs assessed as related to study intervention were ≤Grade 2 except for 1 participant with insomnia, which was Grade 3 in intensity.

Most Cohort 1C participants reported AEs with a maximum of Grade 1 or 2.

No deaths were reported in Study 208580. 1 participant in Cohort 1C (Q8W) experienced a nonfatal SAE of gastritis alcoholic haemorrhagic, which was assessed as not related to the study intervention.

No Cohort 1C participant discontinued study intervention permanently due to an AE.

In Cohort 1C, there were no AESIs reported relevant to the following: post-injection reactions; neuropsychiatric events of suicidal ideation/behaviour, bipolar disorder, psychosis, and mood disorders; hepatotoxicity; pancreatitis; or impact on creatinine. No AESIs were serious. Otherwise in Cohort 1C:

- All ISRs were ≤Grade 2 in intensity, nonserious, and not treatment limiting. Most ISRs were injection site pain.
- There were no AESI leading to withdrawal of study intervention.
- The only AESI that was >Grade 2 in intensity was Grade 3 insomnia (Q4W group), which had an onset the same day as the start of the injection phase. Diphenhydramine was administered, and the participant continued in the study. The insomnia resolved in 5 days.

Assessor's comments

Overall, no new safety concerns emerged from the findings through week 16 of cohort 1C of Study 208580, which enrolled 30 HIV-adolescents' participants who received CAB in addition to cART. Nevertheless, final conclusion is pending assessment from an on-going parallel procedure concerning Vocabria (Procedure No. EMEA/H/C/004976/II/0022).

TOPIC 2 – POST-MARKETING DATA

Patient exposures from marketing exposure

The algorithm used to derive post-approval exposure data for Apretude from IQVIA assumes a standard dose of CAB LA of 1 vial per 2 months. These exposure data do not distinguish between use in adults vs adolescents. IQVIA sales data can be up to 6 months in arrears, and the latest exposure data are available up to 30 June 2023. Based on IQVIA data, cumulative post-approval exposure of CAB LA for PrEP (Apretude) to 30 June 2023 is estimated to be 6 564 patient-years.

Post-marketing case reports

The safety profile for CAB LA is proactively reviewed through ViiV Healthcare's regular and systematic pharmacovigilance processes, including the following: ongoing awareness and review of important individual cases; aggregate analyses of spontaneous ADR reports; trend analysis to detect increased frequency of reporting; quantitative methodologies to detect events disproportionately reported with respect to specific situations (e.g., drug interactions and medication errors) and special populations (e.g., elderly and paediatric); and review of the literature. All signals identified are evaluated, and appropriate action is agreed. The options include continuing routine proactive pharmacovigilance, defining further work to better understand the risk, or recommendation of a label change and/or amendment to the product's risk management plan. The resulting safety profile is maintained and summarized in the Company's corresponding CSI in the GDS and Local Country Labeling.

There were a total of 650 initial or follow-up spontaneous and post-marketing surveillance cases for CAB LA (administered as PrEP) retrieved from the ViiV Healthcare's safety database from the first approval of CAB LA to the last data cut-off of 30 September 2023. Of these cases, 291/650 reported the age of the PrEP user; for 359/650 cases, the age was not reported. In cases where age was reported, the PrEP user was over 18 years old in all cases.

Literature

A review of literature for the period from the first approval of CAB LA to 30 September 2023 did not identify any additional clinical trials assessing use of CAB LA for PrEP. Thus, no new safety concerns in the adolescent population were identified from a review of the literature.

Assessor's comments

When age was available, no reports from adolescents PrEP users were retrieved from the ViiV Healthcare's safety database from the date of first approval of CAB LA to the last data cut-off of 30 September 2023. The MAH stated that no new safety concerns in the adolescent population were identified from a review of the literature.

8.3. Discussion

Safety findings from the CAB PrEP studies: Study 213002 / HPTN 083-01 and Study 213003 / HPTN 084-01 were presented to provide supplemental information supporting the use of CAB LA for PrEP in adolescents weighing at least 35 kg who are at risk of sexually acquired HIV-1 infection. The applicant presented separately the safety data from each of the pivotal studies, HPTN 083-01 and HPTN 084-01, as it concerns adolescent females and males at birth, respectively, as the sub-studies to the parent protocols (HPTN 083 and HPTN 084). There was no treatment randomization due to these studies being a single-arm, open-label. Updated data based on the Study 208580 (MOCHA; IMPAACT 2017)—a study evaluating CAB

treatment for adolescents living with HIV— was also presented by the MAH in this application and provided supportive safety information on the use of CAB in adolescents.

In HPTN 083-01, all 9 participants (100%) received oral study drug in Step 1, 7 (78%) who started Step 2 received all 5 injections, and 8 participants received study drug around the Week 33 visit as planned. In HPTN 084-01, 53 of 55 participants (96%) received oral study drug in Step 1, 52 (98%) who started Step 2 received all 5 injections, all of whom received study drug around the Week 33 visit as planned. The median (min, max) overall exposure to study drug throughout the study was similar across the two studies: 232.0 (36, 239) days in HPTN 083-01 and 231.0 (21, 240) days in HPTN 084-01. Adherence to study drug was high overall among participants in both studies. Although the duration of treatment and especially the sample size are limited, the patient exposure is considered acceptable for the purpose of this application. Of note, and as above mentioned is also the supportive Study 208580 (MOCHA) that provides exposure data for the HIV-adolescent population.

In both HPTN 083-01 and HPTN 084-01 studies, all participants reported at least one AE during Step 1 and/or Step 2, the majority of which were considered by the investigator to be drug-related. Across both studies, there were no drug-related or fatal SAEs and no drug-related AEs or ISRs led to discontinuation of study drug. In HPTN 083-01, most participants reported one or more AEs that were Grade 2 (78%). Grade 3 events were reported by 22% of participants. No participant reported a grade 4 event, and no grade 5 (death) event occurred during the study. In HPTN 084-01, the majority of participants reported one or more AEs that were Grade 2 (78%). Grade 3 events were reported by 16% of participants. One participant reported a Grade 4 event. No Grade 5 (death) events occurred.

In HPTN 083-01, AEs in Steps 1 and 2 were reported most frequently from either the Investigations SOC (9 [100%] participants) or General disorders and administration site conditions SOC (5 [56%] participants). The proportion of participants who had events considered drug-related by the investigator was 56% (n=5). The most frequently reported drug-related AE was injection site pain (n=5). In HPTN 084-01, AEs in Steps 1 and 2 were reported most frequently from either the Investigations SOC (55 [100%] participants) or Infections and infestations SOC (29 [53%] participants). The proportion of participants who had events considered drug-related by the investigator was 37 (67%). The most frequently reported drug-related AE was injection site pain (n=13; 24%).

In what concerns to established AESI for CAB, the following deserve to be mentioned and summarized:

- *Injection site reactions*: overall, injections of CAB PrEP were generally well tolerated in the HPTN 083-01 and HPTN 084-01 populations of adolescents. The nature and severity of ISRs experienced by adolescent participants in these studies are consistent with the known CAB LA safety profile per current product labeling. In HPTN 083-01, a total of 40 injections were administered to the 9 participants who received injections, and 5 participants (56%) experienced 20 ISRs. In HPTN 084-01, a total of 263 injections were administered to the 53 participants who received injections, and 14 participants (26%) experienced 20 ISRs.
- *Hepatotoxicity*: there were no reported events of potential hepatotoxicity AESIs in Step 1 or Step 2 of either HPTN 083-01 or HPTN 084-01.
- *Hypersensitivity reactions*: there were no reported events of potential hypersensitivity reaction AESIs in Step 1 or Step 2 of either HPTN 083-01 or HPTN 084-01.
- *Rash*: in HPTN 083-01, 2 participants (22%) each reported a rash AESI event (rash macular and rash) during the study; for both participants, the event was non-serious, Grade 1, and considered not related to study drug by the investigator, and CAB was continued. In HPTN 084-01, there were no reported events of potential rash AESIs in Step 1 or Step 2 of this study.

- *Neuropsychiatric adverse events*: no new neuropsychiatric concerns were identified in adolescents compared to the known safety profile observed in the adult PrEP studies (HPTN 083/HPTN 084) and current product labeling. In HPTN 083-01, no participant experienced a Suicidal Ideation/Behavior AESI in Step 1 or Step 2. 1 participant experienced 1 event of Suicidal Ideation/Behavior AESI (suicidal ideation) in Step 3, which was reported as serious and not related to study drug. In HPTN 084-01, 1 participant (2%) experienced 1 event of Suicidal Ideation/Behavior AESI (suicide attempt) in Step 2, which was reported as serious and not related to study drug. No participants experienced a Suicidal Ideation/Behavior AESI in Step 1. An additional participant had an AE of suicide attempt during the HPTN 084-01 OLE. 'Suicide ideation and attempt' in adolescents are a special warning in the section 4.4 of CAB PrEP SmPC and are labelled in the section 4.8 of the SmPC with a frequency of uncommon.
- *Seizures and seizure-like events*: there were no reported events of potential Seizures and seizure-like AESIs during either HPTN 083-01 or HPTN 084-01.
- *Hyperglycaemia and diabetes*: in HPTN 083-01, a total of 3 participants (33%) developed 5 events of Hyperglycaemia AESI, all of whom had the PT of hyperglycaemia with a maximum post-Baseline intensity of Grade 1. In HPTN 084-01, a total of 22 participants (40%) developed 31 events of Hyperglycaemia AESI, all of whom had the PT of blood glucose increased with a maximum post-Baseline intensity of Grade 1 for all but 1 event which was Grade 2. Across both studies, there were no serious or drug-related Hyperglycaemia AESIs and no Hyperglycaemia AESIs led to discontinuation of study drug; all participants were reported to have recovered.
- *Weight gain*: there were no reported events of potential Weight gain AESIs during either HPTN 083-01 or HPTN 084-01.
- *Rhabdomyolysis*: although there were no reported AEs consistent with rhabdomyolysis or related AESI terms during Study HPTN 083-01, 1 participant developed a Grade 3 laboratory event of elevated CK. During Study HPTN 084-01, 1 (2%) participant experienced a Rhabdomyolysis AESI (myalgia, during Step 1). This Grade 2 event (myalgia) was considered non-serious and not related to study drug by the investigator.
- *Pancreatitis*: there were no reported events of potential pancreatitis AESIs during either HPTN 083 01 or HPTN 084-01.
- *Impact on creatinine*: in HPTN 083-01, 2 (22%) participants had Blood creatinine increased and 6 (67%) participants had Creatinine renal clearance decreased. All of the reported events were non-serious, =<Grade 2, were not considered related to study drug, and none of them led to study drug discontinuation. In HPTN 084-01, 9 (16%) participants had Blood creatinine increased and 41 (75%) participants had Creatinine renal clearance decreased. All of the reported events were non-serious, most were =<Grade 2, and none of them led to study drug discontinuation. 2 (4%) participants had Grade 3 Blood creatinine increased and 2 (4%) participants had Grade 3 Creatinine renal clearance decreased. These Grade 3 events were not considered related to study drug. There were no Grade 4 or 5 events. For both studies, when laboratory findings for creatinine clearance and creatinine values were taken into account, the magnitude of median post-Baseline change of these laboratory values through Week 34 was not clinically relevant. The observed graded laboratory values did not have a clinical impact on any participants, were not reported with concurrent AEs associated with renal toxicity, nor did they result in study drug discontinuation or dose modification.

Laboratory findings did not show any new safety concerns when compared with CAB PrEP studies for adults. Most emergent clinical chemistry toxicities were of Grade 1 or Grade 2 intensity. There were few emergent clinical chemistry toxicities of Grade 3, and no Grade 4 shifts were reported. In what concerns to clinical hematology no new safety concerns have emerged. In both HPTN 083-01 and HPTN 084-01 studies, no

clinically meaningful trends were noted over the course of the study for either urine glucose or urine protein. In both studies, changes in vital signs, weight and body mass index did not show any new safety concerns.

Overall, no new safety concerns emerged from the findings through week 16 of cohort 1C of supportive Study 208580, which enrolled 30 HIV-adolescents participants who received CAB in addition to cART.

In conclusion, CAB PrEP in adolescents was well-tolerated. Overall, AE data from the HPTN 083-01 and HPTN 084-01 studies in adolescents did not show any new emergent safety concerns when compared with the known safety profile of CAB PrEP for adults (HPTN 083 and HPTN 084 studies).

9. Risk management plan

The MAH submitted/was requested to submit an updated RMP version 1.2 with this application. The (main) proposed RMP changes were the following:

Summary of significant changes in this RMP:		
PART	**MODULE**	**Changes made in the present EU-RMP**
PART II, SAFETY SPECIFICATION	SI Epidemiology of the indication(s) and the target population	Updated epidemiology section
Part II, SIII CLINICAL TRIAL EXPOSURE	SIII Clinical trial exposure	Inclusion of updated clinical trial exposure data, from adolescent 083-01 and 084-01 studies
PART II, SIV POPULATIONS NOT STUDIED IN CLINICAL TRIALS	SIV.2 Limitations to detect adverse reactions in clinical trial development programmes	Clinical trial exposure related information updated
	SIV.3 Limitation in respect to populations typically under represented in clinical trial development programmes	Inclusion of data from adolescent 083-01, 084-01 and MOCHA studies
PART II, SV POST AUTHORISATION EXPERIENCE	SV1.1 Method used to calculate exposure	Inclusion of updated post marketing exposure
	SV1.2 Exposure	
PART II SVII- DETAILS OF IMPORTANT IDENTIFIED RISKS, AND IMPORTANT POTENTIAL	SVII 3.1 Presentation of important Identified and Potential Risks	Hepatotoxicity risk updated with adolescent 083-01 and 084-01 studies

RISKS AND MISSING INFORMATION		
PART III PHARMACOVIGILANCE PLAN (INCLUDING POST AUTHORISATION SAFETY STUDIES	III.2 Additional Pharmacovigilance activities	Updates to study numbers
	III.3 Summary Table of additional Pharmacovigilance activities	Study status and milestone information revised
PART VII ANNEXES	Annex 3	Inclusion of approved APR and EU cohort study protocol
	Annex 7	Updated references linked to Epidemiology section updates

10.1 Safety Specification

Epidemiology of the indications and target population

The MAH updated all subsections of Part II Module SI with available up to date data, which is acknowledged.

However, as regards the subsection "Prevalence of HIV" the proposed amendments are only partly supported by the PRAC-Rapporteur and in line with the guidance document the following should be considered by the MAH:

> *Information on inter-regional (e.g. EU, US, Asia, Africa etc.) variations may be provided when relevant,* ***but the focus should be on the European population.***

Therefore, the MAH is requested to provide appropriate up to date information regarding the prevalence of HIV in the EU in the respective subsection (Prevalence) of Part II Module SI.1.

With the response to the RSI, the MAH updated this section as requested.

Clinical trial exposure

The MAH updated all subsections of Part II Module SIII ´Clinical trial exposure´ with available up to date data for adults and included a new subsection regarding adolescents presenting exposure data from the HPTN 083-01 and HPTN 084-01 studies, which is acknowledged by the PRAC Rapporteur.

Populations not studied in clinical trials

The MAH updated Part II Module SIV.2 "Limitations to detect adverse reactions in clinical trial development programmes" with available up to date data regarding the number of participants which have been exposed to CAB PrEP and accompanied long-term data for CAB PrEP usage ≥3 years, which is acknowledged.

Furthermore, also Part II Module SIV.3 "Limitations in respect to populations typically under- represented in clinical trial development programmes" has been updated by the MAH by including data regarding adolescents below <18 years of age and weighing at least 35 kg which have been exposed to CAB for PrEP. In addition to this, data from adolescents living with HIV have been included. This is also acknowledged by the PRAC-Rapporteur.

Post-authorisation experience

The updated information in Part II Module SV.1.1 ´Method used to calculate exposure´ provided by the MAH is noted. In this regard, the following statement has been newly included:

"Due to the oral cabotegravir tablet being marketed for both HIV-1 treatment and HIV-1 PrEP indications, the exposure of oral cabotegravir PrEP tablets cannot be provided as the sales data is currently combined with the treatment indication."

Additional EU requirements for the safety specification

Within the currently submitted RMP version 1.2, the MAH did not propose any updates to RMP Part II Module SVI ´Additional EU requirements for the safety specification´, which is acknowledged.

Identified and potential risks

Important identified risks: Hepatotoxicity, HIV-1 seroconversion and Development of resistance

The MAH updated Part II Module SVII.3.1´Presentation of important identified risks and important potential risks´ regarding the important identified risks "Hepatotoxicity"; "HIV-1 seroconversion" and "Development of resistance" with available up to date data regarding the adolescent population from the HPTN 083-01 and HPTN 084-01 studies.

Important potential risk: Medication errors including treatment non-compliance

Regarding the important potential risk "Medication errors including treatment non-compliance" the MAH provide a small update with the following sentence:

"In the HPTN 083-01 and 084-01 adolescent studies there was high adherence overall among participants."

In this regard, it should be noted, that CAB for PrEP is already authorised in adults and adolescents, weighing at least 35 kg.

10.2 Summary of the safety concerns

Table SVIII.1: Summary of the Safety Concerns

Summary of safety concerns	
Important identified risks	Hepatotoxicity
	HIV-1 seroconversion
	Development of resistance: • In participants starting CAB with unrecognized or acute HIV-1 infection • Due to breakthrough HIV-1 infection while on CAB OLI or LA and delayed diagnosis • Potential risk of HIV-1 acquisition occurring during 'PK tail' and diagnosis is delayed, or effective ARV is not started timely
Important potential risks	Medication errors including treatment non-compliance
Missing information	Use in pregnancy and breastfeeding

No updates to RMP Part II Module SVIII ´Summary of the safety concerns´ are proposed by the MAH, which is currently supported by the PRAC-Rapporteur.

Considering the data in the safety specification, the safety concerns listed above are appropriate.

10.3 Pharmacovigilance plan

Study (Status)	**Summary of objectives**	**Safety concerns addressed**	**Milestones**	**Due dates**
Category 1 - Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorization				
None				
Category 2 – Imposed mandatory additional pharmacovigilance activities which are Specific Obligations in the context of a conditional marketing authorization under exceptional circumstances				
None				
Category 3- Required additional pharmacovigilance activities				

Study **(Status)**	**Summary of objectives**	**Safety concerns addressed**	**Milestones**	**Due dates**
CAB LA PrEP EU Cohort Study to Assess Adherence and Effectiveness, and Monitor for Safety and Resistance ~~Planned~~ Ongoing	This 5-year prospective, non-interventional study will aim to better understand the population receiving CAB LA for PrEP in routine clinical practice, usage patterns, adherence, post marketing clinical effectiveness and seroconversion, discontinuations, and monitor for resistance among seroconverted individuals.	Hepatotoxicity HIV-1 seroconversion Development of resistance: • In participants starting CAB with unrecognized or acute HIV-1 infection • Due to breakthrough HIV-1 infection while on CAB OLI or LA and delayed diagnosis • Potential risk of HIV-1 acquisition occurring during 'PK tail' and diagnosis is delayed, or effective ARV is not started timely Medication errors including treatment non-compliance	~~Draft protocol submission~~	~~3 months after marketing authorisation.~~
			~~Estimated Study start~~	~~EMA/PRAC approval of protocol and CAB LA being commercially available~~
			Final report	~~To be defined after EMA/PRAC approval of protocol~~ Estimated June 2030
The Antiretroviral Pregnancy Registry (APR) to monitor CAB LA PrEP use in Pregnancy ~~Planned~~ Ongoing	The APR is an international registry that monitors prenatal exposures to antiretroviral (ARV) drugs to detect a potential increase in the risk of birth defects through a prospective exposure registration cohort. The registry's primary objective is to monitor for birth defects among ARV exposed pregnancies. The registry has been monitoring pregnancies with prenatal exposure to ARVs used for PrEP since the approval of ARVs used in oral PrEP.	Use in pregnancy	Interim Report 1 (25 pregnancies) ~~Draft protocol Submission~~	Estimated - December 2024 ~~3 months after marketing authorisation~~
			Interim Report 2 (100 Pregnancies) ~~Estimated Study start~~	Estimated – December, 2026 ~~EMA/PRAC approval of protocol and CAB LA being commercially available~~
			Interim Report 3 (200 Pregnancies)	Estimated – December, 2028 Estimated -

Study (Status)	Summary of objectives	Safety concerns addressed	Milestones	Due dates
	The APR is a MAH-sponsored study involving the collaborative effort of multiple companies. Data from the APR will assess maternal (pregnancy outcomes, abortions, still births) and foetal outcomes (premature births and low birth weight) following CAB LA PrEP use during pregnancy. Exposure to CAB LA PrEP relative to gestation period and conception will be captured in the registry, thus enabling assessment of pre-conception exposures along with first, second and third trimester exposures.		~~Interim Report 1 (25 pregnancies)~~	December 2024
			Final report ~~Interim Report 2 (100 Pregnancies)~~ ~~Interim Report 3 (200 Pregnancies)~~ ~~Final report~~ ~~Regular updates~~	Estimated – December, 2029 ~~Estimated – December, 2026~~ ~~Estimated – December, 2028~~ ~~Estimated – December, 2029~~ ~~A registry interim report is prepared semi-annually summarising the aggregate data. Data from the APR will be presented in the CAB PrEP PSUR/PBRER~~

The MAH amended the milestones for the category 3 study regarding ´Pregnancy ´ in line with the other CAB product - Vocabria for HIV therapy, as requested by the PRAC Rapporteur.

No other relevant updates to RMP Part III ´Pharmacovigilance Plan (including post-authorisation safety studies)' are currently proposed by the MAH. In this context it should be noted, that Study 221935 CAB LA PrEP EU Cohort Study already includes individuals weighing ≥35 kg, initiating CAB LA PrEP, in real world clinical setting.

However, the study status for the APR, currently outlined in the table as "planned", should be changed to "ongoing" as the protocol appears already approved and the first interim report is being expected in December 2024 (**RSI**).

With the response to the RSI, the MAH amended PART III.3 as requested. Furthermore, amendments to study 221935 were made. This is supported.

Overall conclusions on the PhV Plan

The proposed post-authorisation PhV development plan is sufficient to identify and characterise the risks of the product.

Plans for post-authorisation efficacy studies

N/A

10.4 Risk minimisation measures

Routine risk minimisation measures

Table Part V.1: Description of routine risk minimisation measures by safety concern

Safety concern	**Routine risk minimization activities**
Hepatotoxicity	**Routine risk communication:** • SmPC section 4.4, 4.8. • Patient Leaflet (PL) section 2 & 4. **Routine risk minimisation activities recommending specific clinical measures to address the risk:** • Recommendation for liver chemistry monitoring are included in SmPC section 4.4 **Other routine risk minimisation measures beyond the Product Information:** This is a prescription only medicine.
HIV-1 Seroconversion	**Routine risk communication:** • SmPC section 4.4 • PL section 2 **Routine risk minimisation activities recommending specific clinical measures to address the risk:** • Individuals should be re-confirmed to be HIV-negative at each injection visit **Other routine risk minimisation measures beyond the Product Information**: This is a prescription only medicine

Development of resistance: In participants starting CAB with unrecognized or acute HIV-1 infection Due to breakthrough HIV-1 infection while on CAB OLI or LA and delayed diagnosis Potential risk of HIV-1 acquisition occurring during 'PK tail' and diagnosis is delayed or effective ARV is not started timely	**Routine risk communication:** • SmPC section 4.4, 4.8 • PL section 2 **Routine risk minimisation activities recommending specific clinical measures to address the risk:** • Individuals should be re-confirmed to be HIV-negative at each injection visit **Other routine risk minimisation measures beyond the Product Information:** This is a prescription only medicine.
Medication errors including treatment non-compliance	**Routine risk communication** • SmPC section 4.2, 4.4 • PL section 2 & 3 **Routine risk minimisation activities recommending specific clinical measures to address the risk:** None **Other routine risk minimisation measures beyond the Product Information:** This is a prescription only medicine.
Use in Pregnancy and breastfeeding	**Routine risk communication:** • SmPC section 4.6. • PL section 2 **Routine risk minimisation activities recommending specific clinical measures to address the risk:** None **Other routine risk minimization measures beyond the Product Information:** This is a prescription only medicine

No updates to RMP Part V.1 ´Routine risk minimisation measures´ are proposed by the MAH, which is supported by the PRAC-Rapporteur

Additional risk minimisation measures

The key messages from the educational materials listed below are provided in ANNEX 6.

The education materials comprise of the following:

- Guide for prescribers
- Guide for individuals at risk
- Prescribers' Checklist
- Reminder Card for individuals at risk

No updates to RMP Part V.2 ´Additional risk minimisation measures´ are proposed by the MAH, which is supported by the PRAC-Rapporteur

Overall conclusions on risk minimisation measures

The proposed risk minimisation measures are sufficient to minimise the risks of the product in the proposed indication(s).

10.5 Elements for a public summary of the RMP

The elements for a public summary of the RMP do not require revision following the conclusion of the procedure.

10.6 Annexes

The MAH amended Annex 3 with the approved APR + Study 221935 protocols and Annex 7 with references linked to Epidemiology section. Furthermore, Annex 2 have been amended in line with Part III.3.

10.7 Overall conclusion on the RMP

☒ The changes to the RMP are acceptable.

The MAH is reminded that in case of a Positive Opinion, the body of the RMP and Annexes 4 and 6 (as applicable) will be published on the EMA website at the time of the EPAR publication, so considerations should be given on the retention/removal of Personal Data (PD) and identification of Commercially Confidential Information (CCI) in any updated RMP submitted throughout this procedure.

10. Changes to the Product Information

As a result of this variation, sections 4.8 and 5.2 of the SmPC are being updated to include data from clinical studies in HIV-1 uninfected adolescents (HPTN 083-01 and HPTN 084-01), updated data from the MOCHA study (final analysis of Cohort 1C at Week 16) and updated PK data based on a population PK analysis of cabotegravir in adolescents in MOCHA, HPTN 083-01 and HPTN 084-01.

With regards to the proposed update of section 5.1, the CHMP considered that the following paragraph

HPTN 083-01 and HPTN 084-01

In studies HPTN 083-01 and HPTN 084-01, there were no incident infections observed among 64 at-risk

adolescents (weighing ≥ 35 kg) receiving cabotegravir for HIV-1 PrEP.

was not relevant for the prescribers. In particular, the fact that none of the 64 adolescent participants included in study HTN083-01 and HTN084-01 developed an HIV infection is as expected and does not provide more insight into Apretude.

Section 4.2 of the SmPC is also being updated to improve and clarify the wording related to missed doses of oral PrEP and renal impairment.

The Package Leaflet was updated to revise the list of local representatives.

Changes are also made to the PI to bring it in line with the current QRD template version 10.4.

11. Request for supplementary information

11.1. Other concerns

Clinical aspects

Pharmacokinetics

Given the absence of the report on the updated PopPK model (Document No. TMF-16443596), it is not possible to ensure the validity and reliability of the model parameters and their impact on the final simulations included in the SmPC. Specifically, the applicant should comment on:

- The relevance of the optimized weight allometry exponents for V and Cl
- The questionable quality of the VPCs for Studies 213002 and 213003, and the apparent discrepancy where the median and 5th percentile of the simulated data do not capture the observed data well
- VPCs for data from study 208580 should also be presented.

Finally, what are the implications of these issues for the final simulations and their inclusion in the SmPC?

RMP aspects

1. The MAH is requested to provide appropriate up to date information regarding the prevalence of HIV in the EU in the respective subsection of Part II Module SI.1.

2. The study status for the APR should be changed to "ongoing" within table III.3 of the Pharmacovigilance Plan.

SmPC aspects

Comments to the SmPC are in attachment. Please revise section 5.1. to delete the sentence:

HPTN 083-01 and HPTN 084-01

In studies HPTN 083-01 and HPTN 084-01, there were no incident infections observed among 64 at-risk adolescents (weighing ≥ 35 kg) receiving cabotegravir for HIV-1 PrEP.

This sentence is not considered relevant for the prescribers. The fact that none of the 64 adolescent participants included in study HTN083-01 and HTN084-01 developed an HIV infection is as expected and does not provide more insight into Apretude.

12. Assessment of the responses to the request for supplementary information

12.1. Other concerns

Clinical aspects

Pharmacokinetics

Question

Given the absence of the report on the updated PopPK model (Document No. TMF-16443596), it is not possible to ensure the validity and reliability of the model parameters and their impact on the final simulations included in the SmPC. Specifically, the applicant should comment on:

- The relevance of the optimized weight allometry exponents for V and Cl
- The questionable quality of the VPCs for Studies 213002 and 213003, and the apparent discrepancy where the median and 5th percentile of the simulated data do not capture the observed data well
- VPCs for data from study 208580 should also be presented.

Finally, what are the implications of these issues for the final simulations and their inclusion in the SmPC?

Summary of the MAH's response

The report on the updated PopPK model (Document No. TMF-16443596) is provided with the response package.

Information regarding the queries is provided here below:

- The relevance of the optimized weight allometry exponents for V and Cl

The original tNDA PopPK model implemented baseline body weight scaling on CL/F, V2/F, Q/F, and V3/F with estimated exponents (body weight on CL/F and Q/F was 0.618, and effect of body weight on V2/F and V3/F was 0.702; GSK Document No.:2018N384611_01). This model was used to derive the adult exposure parameters that are included in the current SmPC. The bodyweight range of the adult data included in the model was. 41.2-168.3 kg, which covered most of the adolescent bodyweight range (Table 37).

A sensitivity analysis was performed to assess the impact of fixing exponents to standard values of 0.75 and 1 for all clearance and volume of distribution parameters. Fixing the exponent to the standard allometric exponents led to an increase in OFV of 39.4 points (GSK Document No.:TMF-16443596). This result was similar to what had been observed with final adult PopPK model (tNDA PopPK), where fixing exponents led to an increase in the objective function. The conclusion, therefore, based on the totality of both the adult and adolescent data, was to use the model with estimated allometric exponents to derive all post-hoc exposure metrics, consistent with what had been done with the adult exposures presented in the current SmPC. The final estimated allometric exponents with all adult and adolescent data on bodyweight on CL/F and Q/F and on V2/F and V3/F were similar to previous adult values.

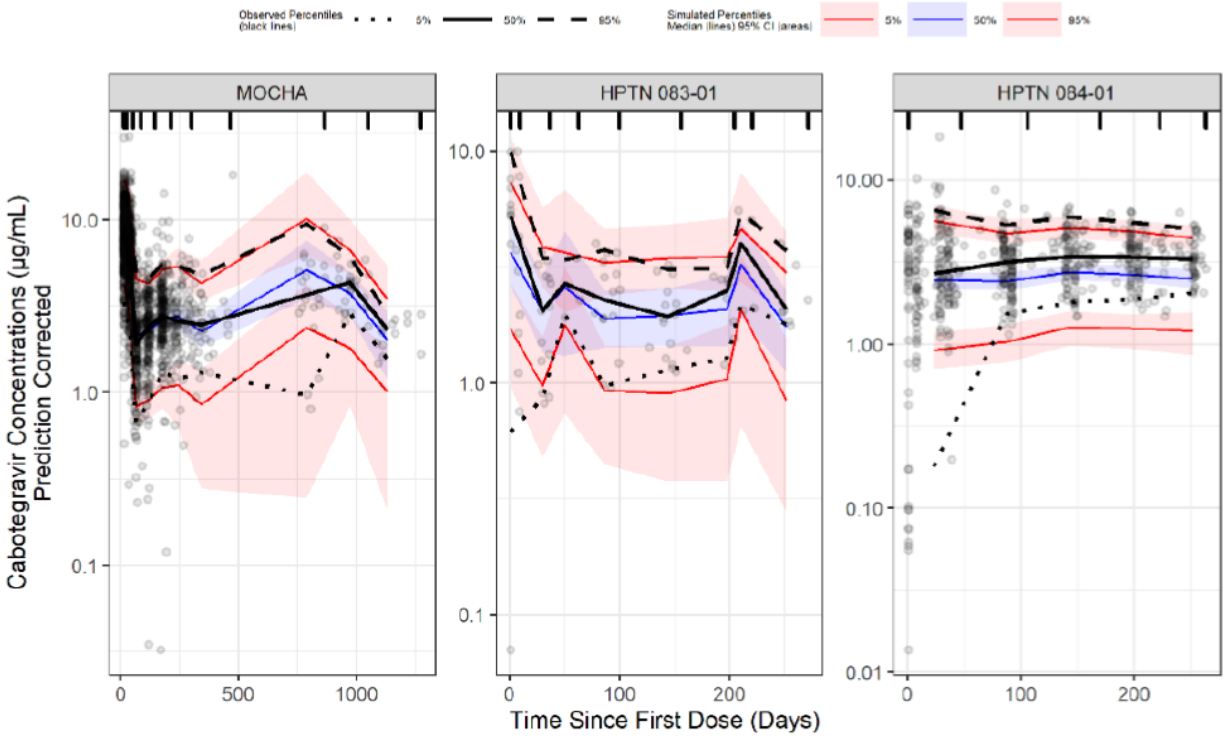
Table 37. Demographic characteristics in the adolescent and overall popilations

	Adult studies (N=1647)	HPTN 083-01 (N=9)	HPTN 084-01 (N=53)	IMPAACT 2017 (N=147)	Overall adolescents (N=209)	Overall population (N=1856)
Female	424 (25.7%)	0 (0%)	53 (100%)	75 (51.0%)	128 (61.2%)	552 (29.7%)
BMI (kg/m^2) Median [min, max]	25.4 [15.3, 69.5]	21.6 [20.0, 51.6]	22.2 [15.8, 34.1]	19.4 [16.0, 33.9]	20.4 [15.8, 51.6]	24.7 [15.3, 69.5]
Weight (kg) Median [min, max]	76.6 [41.2, 168]	70.6 [63.0, 167]	55.5 [39.9, 80.8]	47.7 [35.2, 98.5]	50.8 [35.2, 167]	74.8 [35.2, 168]

- The questionable quality of the VPCs for Studies 213002 and 213003, and the apparent discrepancy where the median and 5th percentile of the simulated data do not capture the observed data well

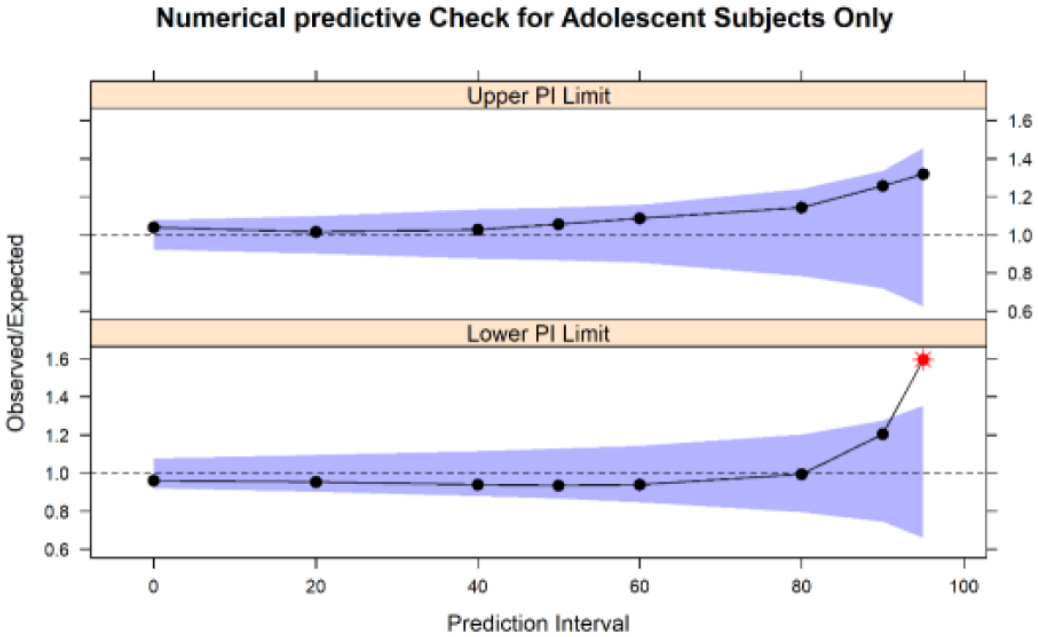
The final PopPK model was evaluated by a pcVPC and NPC. The VPCs for Studies with adolescent population are presented in TMF-16443596 – Figure 12 - and reported here below (Figure 1). The final PopPK model was able to capture the observed median, 5th and 95th percentiles of CAB concentrations with sufficient accuracy. The observed percentiles for Studies 208580 (MOCHA), 213002 (HPTN 083-01) were mostly consistent with the simulated percentiles or contained within the 95% CI. The observed median and 5th percentile for Study 213003 (HPTN 084-01) were higher than simulated percentiles, but the observed concentrations were within the 90% prediction intervals. The numerical predictive (NPC) confirms these results, showing the model adequately described the data between the observations and model predictions across all percentiles. NPC for Studies 208580 (MOCHA), 213002 (HPTN 083-01), and 213003 (HPTN 084-01) is presented in Figure 2. These results were used to justify the adequacy of the model to be used for simulations, as it was expected that simulations would capture the range of expected concentrations which then could be compared to safety and efficacy margins of interest established from the adult indication.

Figure 1: pcVPC of the final CAB PopPK model stratified by study group (Run11)



Notes: The open circles represent the observed data. The solid black lines represent the median of the observed data, and the dashed lines represent the 5th and 95th percentiles of the observed data. The blue solid lines represent the median of the simulated data, and the pink solid lines represent the 5th and 95th percentiles of the simulated data. The blue and pink shaded areas represent the 95% CI of the median and the 5th and 95th percentiles of the simulated data, respectively.
MOCHA=Study 208580; HPTN 083-01=Study 213002; HPTN 084-01=Study 213003.
Abbreviations: CAB=cabotegravir; CI=confidence interval; pcVPC=prediction-corrected visual predictive check; PopPK=population pharmacokinetic(s)

Figure 2: NPC of the final CAB PopPK model



Notes: The connected black dots represent the ratio of the number of observations that are outside their own prediction interval.
The blue shaded area is the 95% PI for this ratio, and the red dot is an outlier ratio.
Only adolescent participants from Studies 208580 (MOCHA), 213002 (HPTN 083-01), and 213003 (HPTN 084-01) are included.
Abbreviations: CAB=cabotegravir; NPC=numerical predictive check; PI=prediction interval; PopPK=population pharmacokinetic

- VPCs for data from study 208580 should also be presented.

VPCs for data from study 208580 are also presented in Figure 1.

- Implications of these issues for the final simulations and their inclusion in the SmPC

- The exposure metrics presented in Table 7 (reference: Apretude Type II variation assessment report RSI; Procedure No. EMEA/H/C/005756/II/0004), were derived from the individual post hoc estimates from adolescents in final PopPK model (GSK Document No.:TMF-16443596). The goodness of fit plots (Figure 8 GSK Document No.:TMF-164435960) and individual fits (Figure 40 GSK Document No.:TMF-16443596) show the model describing the observed plasma concentration-time data well; thus post hoc estimates derived from the model were considered appropriate to use for describing post hoc exposures. The exposure metrics proposed for the SmPC are presented in the exposure metrics in Table 7 (reference: Apretude Type II variation assessment report RSI; Procedure No. EMEA/H/C/005756/II/0004), and thus are considered representative of what would be expected following proposed dosing regimen of cabotegravir for PrEP.

- No additional simulations are included in the SmPC, but as described above and in the PopPK report (GSK Document No.:TMF-16443596), the model has been shown to capture the range of observed adolescent data across all studies, and thus additional simulations included in both reports (GSK Document No.:TMF-16443596 and TMF-17066669) comparing exposures range of adolescents to adults are appropriate and justify dose adjustment of the approved Apretude dosing regimen in adolescents weighing at least 35kg.

Assessment of the MAH's response

The applicant provided the requested report. It was observed that the adjustment of the initial model developed with the adult data to the additional paediatric data resulted in very similar model parameters

with percentual differences that are generally lower than 10% except in some IIV and covariance parameters. In particular, the changes in the exponents on the body wight scaling on CL/F and V/F parameters changed from the original ones, determined on the adult data. The applicant referred that fixing the exponents to standard values of 0.75 and 1 for CL and V led to an increase in OFV and, thus, justified its adjustments. Also, since the overall population included subjects with body weights from 35.2 to 168 kg and the simulations are mainly describing the PK within this same population (not extrapolating to younger and smaller populations), this is acceptable. Regarding the quality of the model, as judged by the GOF and VPCs, it can be considered acceptable. Only the VPC of study 084-01 showed some underprediction of the median data that is not seen in the remaining studies and the NPC results suggest that the model adequately described the data between the observations and model predictions across all percentiles. Taking all in consideration, the final model seems adequate for the intended purpose.

Conclusion

The final popPK model was considered adequate for the intended purpose. Point resolved

RMP aspects

1. The MAH is requested to provide appropriate up to date information regarding the prevalence of HIV in the EU in the respective subsection of Part II Module SI.1.

Summary of the MAH's response

The MAH has updated Part II Module SI.1 of the cabotegravir PrEP EU RMP with EU prevalence information, in RMP version 1.2 which is provided with this response document.

Assessment of the MAH's response

The MAH has amended Part II Module SI.1 as requested.

Conclusion

Issue solved.

2. The study status for the APR should be changed to "ongoing" within table III.3 of the Pharmacovigilance Plan.

Summary of the MAH's response

The MAH has amended study status for the Antiretroviral Pregnancy study from planned to ongoing in Table III.3 of the cabotegravir PrEP EU RMP in RMP version 1.2. In addition, during the type 2 variation procedure, the EMA approval of the procedure for assessment of the protocol for PV Plan EU Cohort study 221935 (EMEA/H/C/005756) has also completed and corresponding minor administrative updates are reflected in EU RMP version 1.2.

Assessment of the MAH's response

The MAH amended RMP Part III.3 as requested. Furthermore, amendments to study 221935 were made. This is supported by the Rapporteur.

However, within the next regulatory opportunity the follow-up period especially of seroconverters from study 221935 should be amended as approved during the protocol finalisation in procedure EMEA/H/C/005756/MEA/003.1.

Conclusion

Issue solved for this procedure.

SmPC aspects

Question

Please revise section 5.1. to delete the sentence:

HPTN 083-01 and HPTN 084-01

In studies HPTN 083-01 and HPTN 084-01, there were no incident infections observed among 64 at-risk adolescents (weighing ≥ 35 kg) receiving cabotegravir for HIV-1 PrEP.

This sentence is not considered relevant for the prescribers. The fact that none of the 64 adolescent participants included in study HTN083-01 and HTN084-01 developed an HIV infection is as expected and does not provide more insight into Apretude.

Summary of the MAH's response

The MAH deleted the sentence as requested.

Assessment of the MAH's response

The MAH's response is considered acceptable.